

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representation of
The original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

This Page Blank (uspto)



Europäisches
Patentamt

European
Patent Office

Office européen
des brevets

PCT/GB 99/03295

97806836

REC'D 08 DEC 1999

WIPO

PCT

Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

98402496.8

PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

DEN HAAG, DEN
THE HAGUE,
LA HAYE, LE

23/11/99

This Page Blank (uspto)



Europäisches
Patentamt

European
Patent Office

Office européen
des brevets

Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.:
Demande n°: 98402496.8

Anmeldetag:
Date of filing: 08/10/98
Date de dépôt:

Anmelder:
Applicant(s):
Demandeur(s):
ZENECA LIMITED
London W1Y 6LN
UNITED KINGDOM
Zeneca-Pharma SA
51689 Reims Cedex 2

FRANCE
Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
Quinazoline derivatives

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat:
State:
Pays:

Tag:
Date:
Date:

Aktenzeichen:
File no.
Numéro de dépôt:

Internationale Patentklassifikation:
International Patent classification:
Classification internationale des brevets:

/

Am Anmeldetag benannte Vertragsstaaten:
Contracting states designated at date of filing: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE
Etats contractants désignés lors du dépôt:

Bemerkungen:
Remarks:
Remarques:

This Page Blank (uspto)

98/022

- 1 -

QUINAZOLINE DERIVATIVES

The present invention relates to quinazoline derivatives, processes for their preparation, pharmaceutical compositions containing them as active ingredient, methods for the treatment of disease states associated with angiogenesis and/or increased vascular permeability, to their use as medicaments and to their use in the manufacture of medicaments for use in the production of antiangiogenic and/or vascular permeability reducing effects in warm-blooded animals such as humans.

Normal angiogenesis plays an important role in a variety of processes including embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). Alteration of vascular permeability is thought to play a role in both normal and pathological physiological processes (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al, 1993, Cancer and Metastasis Reviews, 12: 303-324). Several polypeptides with in vitro endothelial cell growth promoting activity have been identified including, acidic and basic fibroblast growth factors (aFGF & bFGF) and vascular endothelial growth factor (VEGF). By virtue of the restricted expression of its receptors, the growth factor activity of VEGF, in contrast to that of the FGFs, is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman et al, 1993, Endocrinology, 133: 848-859; Kolch et al, 1995, Breast Cancer Research and Treatment, 36:139-155) and vascular permeability (Connolly et al, 1989, J. Biol. Chem. 264: 20017-20024). Antagonism of VEGF action by sequestration of VEGF with antibody can result in inhibition of tumour growth (Kim et al, 1993, Nature 362: 841-844). Basic FGF (bFGF) is a potent stimulator of angiogenesis (e.g. Hayek et al, 1987, Biochem. Biophys. Res. Commun. 147: 876-880) and raised levels of FGFs have been found in the serum (Fujimoto et al, 1991, Biochem. Biophys. Res. Commun. 180: 386-392) and urine (Nguyen et al, 1993, J. Natl. Cancer. Inst. 85: 241-242) of patients with cancer.

Receptor tyrosine kinases (RTKs) are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules

characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in stimulation of the receptor-associated tyrosine kinase activity which leads to phosphorylation of tyrosine residues on both the receptor and other

5 intracellular molecules. These changes in tyrosine phosphorylation initiate a signalling cascade leading to a variety of cellular responses. To date, at least nineteen distinct RTK subfamilies, defined by amino acid sequence homology, have been identified. One of these subfamilies is presently comprised by the *fms*-like tyrosine kinase receptor, Flt or Flt1, the kinase insert domain-containing receptor, KDR (also referred to as Flk-1), and another

10 *fms*-like tyrosine kinase receptor, Flt4. Two of these related RTKs, Flt and KDR, have been shown to bind VEGF with high affinity (De Vries et al, 1992, Science 255: 989-991; Terman et al, 1992, Biochem. Biophys. Res. Comm. 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.

15 The present invention is based on the discovery of compounds that surprisingly inhibit the effects of VEGF, a property of value in the treatment of disease states associated with angiogenesis and/or increased vascular permeability such as cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, endometriosis,

20 dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. Compounds of the present invention generally possess higher potency against VEGF receptor tyrosine kinase than against epidermal growth factor (EGF) receptor tyrosine kinase. Compounds of the invention which have been tested possess activity against VEGF receptor tyrosine kinase such that they may be used in an amount sufficient to inhibit VEGF receptor

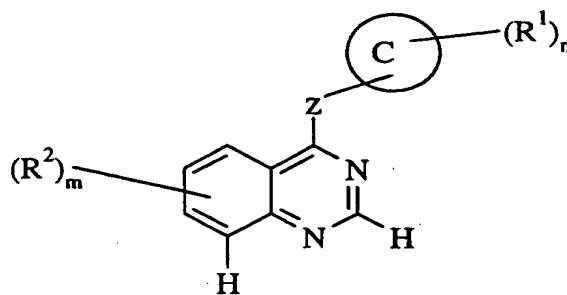
25 tyrosine kinase whilst demonstrating no significant activity against EGF receptor tyrosine kinase. Compounds of the present invention generally possess higher potency against VEGF receptor tyrosine kinase than against FGF R1 receptor tyrosine kinase. Compounds of the invention which have been tested possess activity against VEGF receptor tyrosine kinase such that they may be used in an amount sufficient to inhibit VEGF receptor tyrosine kinase whilst

30 demonstrating no significant activity against FGF R1 receptor tyrosine kinase.

According to one aspect of the present invention there is provided the use of compounds of the formula I:

98/022

- 3 -



(I)

10 wherein:

ring C is a 5-6-membered heterocyclic moiety which may be saturated or unsaturated, which may be aromatic or non-aromatic, and which contains 1-3 heteroatoms selected independently from O, N and S;

Z is -O-, -NH-, -S- or -CH₂-;

15 R¹ represents hydrogen, C₁₋₄alkyl, C₁₋₄alkoxymethyl, di(C₁₋₄alkoxy)methyl, C₁₋₄alkanoyl, trifluoromethyl, cyano, amino, C₂₋₅alkenyl, C₂₋₅alkynyl, a phenyl group, a benzyl group or a 5-6-membered heterocyclic group with 1-3 heteroatoms, selected independently from O, S and N, which heterocyclic group may be aromatic or non-aromatic and may be saturated (linked via a ring carbon or nitrogen atom) or unsaturated (linked via a ring carbon

20 atom), and which phenyl, benzyl or heterocyclic group may bear on one or more ring carbon atoms up to 5 substituents selected from hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, cyano, amino, nitro, C₂₋₄alkanoyl, C₁₋₄alkanoylamino, C₁₋₄alkoxycarbonyl, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphinyl, C₁₋₄alkylsulphonyl, carbamoyl, N-C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl, N,N-di(C₁₋₄alkyl)aminosulphonyl, C₁₋₄alkylsulphonylamino, and a saturated heterocyclic

25 group selected from morpholino, thiomorpholino, pyrrolidinyl, piperazinyl, piperidinyl imidazolidinyl and pyrazolidinyl, which saturated heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, cyano, amino, nitro and C₁₋₄alkoxycarbonyl;

30 n is an integer from 0 to 5;

m is an integer from 0 to 3;

- R^2 represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylsulphonyl, $-NR^3R^4$ (wherein R^3 and R^4 , which may be the same or different, each represents hydrogen or C_{1-3} alkyl), or R^5X^1 - (wherein X^1 represents a direct bond, $-O-$, $-CH_2-$, $-OCO-$, carbonyl, $-S-$, $-SO-$, $-SO_2-$, $-NR^6CO-$, $-CONR^7-$, $-SO_2NR^8-$, $-NR^9SO_2-$ or $-NR^{10}-$ (wherein R^6 , R^7 , R^8 , R^9 and R^{10} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl), and R^5 is selected from one of the following eighteen groups:
- 1) hydrogen or C_{1-5} alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino;
 - 2) C_{1-5} alkyl X^2COR^{11} (wherein X^2 represents $-O-$ or $-NR^{12}-$ (in which R^{12} represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{11} represents C_{1-3} alkyl, $-NR^{13}R^{14}$ or $-OR^{15}$ (wherein R^{13} , R^{14} and R^{15} which may be the same or different each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl));
 - 3) C_{1-5} alkyl X^3R^{16} (wherein X^3 represents $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-OCO-$, $-NR^{17}CO-$, $-CONR^{18}-$, $-SO_2NR^{19}-$, $-NR^{20}SO_2-$ or $-NR^{21}-$ (wherein R^{17} , R^{18} , R^{19} , R^{20} and R^{21} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{16} represents hydrogen, C_{1-3} alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3} alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4} alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl and C_{1-4} alkoxy);
 - 4) C_{1-5} alkyl X^4C_{1-5} alkyl X^5R^{22} (wherein X^4 and X^5 which may be the same or different are each $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{23}CO-$, $-CONR^{24}-$, $-SO_2NR^{25}-$, $-NR^{26}SO_2-$ or $-NR^{27}-$ (wherein R^{23} , R^{24} , R^{25} , R^{26} and R^{27} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{22} represents hydrogen or C_{1-3} alkyl);
 - 5) R^{28} (wherein R^{28} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl and C_{1-4} alkylsulphonyl C_{1-4} alkyl);
 - 6) C_{1-5} alkyl R^{28} (wherein R^{28} is as defined hereinbefore);
 - 7) C_{2-5} alkenyl R^{28} (wherein R^{28} is as defined hereinbefore);
 - 8) C_{2-5} alkynyl R^{28} (wherein R^{28} is as defined hereinbefore);

98/022

- 5 -

9) R^{29} (wherein R^{29} represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents on an available carbon atom selected from hydroxy, halogeno, amino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, trifluoromethyl, cyano, $-CONR^{30}R^{31}$ and $-NR^{32}COR^{33}$ (wherein R^{30} , R^{31} , R^{32} and R^{33} , which may be the same or different, each represents hydrogen, C_{1-4} alkyl or C_{1-3} alkoxy C_{2-3} alkyl));

10) C_{1-5} alkyl R^{29} (wherein R^{29} is as defined hereinbefore);

11) C_{2-5} alkenyl R^{29} (wherein R^{29} is as defined hereinbefore);

12) C_{2-5} alkynyl R^{29} (wherein R^{29} is as defined hereinbefore);

13) C_{1-5} alkyl X^6R^{29} (wherein X^6 represents $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{34}CO-$, $-CONR^{35}-$, $-SO_2NR^{36}-$, $-NR^{37}SO_2-$ or $-NR^{38}-$ (wherein R^{34} , R^{35} , R^{36} , R^{37} and R^{38} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{29} is as defined hereinbefore);

14) C_{2-5} alkenyl X^7R^{29} (wherein X^7 represents $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{39}CO-$, $-CONR^{40}-$, $-SO_2NR^{41}-$, $-NR^{42}SO_2-$ or $-NR^{43}-$ (wherein R^{39} , R^{40} , R^{41} , R^{42} and R^{43} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{29} is as defined hereinbefore);

15) C_{2-5} alkynyl X^8R^{29} (wherein X^8 represents $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{44}CO-$, $-CONR^{45}-$, $-SO_2NR^{46}-$, $-NR^{47}SO_2-$ or $-NR^{48}-$ (wherein R^{44} , R^{45} , R^{46} , R^{47} and R^{48} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{29} is as defined hereinbefore);

16) C_{1-3} alkyl X^9C_{1-3} alkyl R^{29} (wherein X^9 represents $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{49}CO-$, $-CONR^{50}-$, $-SO_2NR^{51}-$, $-NR^{52}SO_2-$ or $-NR^{53}-$ (wherein R^{49} , R^{50} , R^{51} , R^{52} and R^{53} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{29} is as defined hereinbefore); and

17) C_{1-3} alkyl X^9C_{1-3} alkyl R^{28} (wherein X^9 and R^{28} are as defined hereinbefore);

and salts thereof, and prodrugs thereof for example esters, amides and sulphides, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

Preferably ring C is a 5-6-membered heteroaromatic moiety which contains 1-3 heteroatoms selected independently from O, N and S.

More preferably ring C is a 5-membered heteroaromatic moiety which contains 1-3 heteroatoms selected independently from O, N and S.

Preferably Z is $-O-$ or $-S-$, especially $-O-$.

98/022

- 6 -

Preferably R^1 represents a phenyl group, a benzyl group or a 5-6-membered heteroaromatic group with 1-3 heteroatoms, selected independently from O, S and N, (linked via a ring carbon atom), which phenyl, benzyl or heteroaromatic group may be substituted as defined hereinbefore. Preferred 5-6-membered heteroaromatic groups contain one or two N atoms (for example, pyrrole, pyridine, pyrazole, imidazole, pyrimidine, pyrazine and pyridazine), two N atoms and one S atom (for example 1,2,5- and 1,3,4-thiadiazole), one N and one O atom (for example oxazole, isoxazole and oxazine), one N and one S atom (for example thiazole and isothiazole) and one O or one S atom (furan and thiophene).

More preferably R^1 is a phenyl group or a 5-6-membered heteroaromatic group with 1-3 heteroatoms, selected independently from O, S and N, (linked via a ring carbon atom), which phenyl or heteroaromatic group is optionally substituted as hereinbefore defined.

Especially R^1 is phenyl optionally substituted as hereinbefore defined.

Preferably the substituents on an available ring carbon atom in R^1 are selected independently from halogeno, C_{1-2} alkyl, C_{1-2} alkoxy, trifluoromethyl, cyano, nitro, C_{2-3} alkanoyl, C_{1-3} alkanoylamino, C_{1-3} alkoxycarbonyl, C_{1-3} alkylsulphanyl, C_{1-3} alkylsulphinyl, C_{1-3} alkylsulphonyl, carbamoyl, N - C_{1-3} alkylcarbamoyl, N,N -di(C_{1-3} alkyl)carbamoyl, aminosulphonyl, N - C_{1-3} alkylaminosulphonyl, N,N -di(C_{1-3} alkyl)aminosulphonyl, C_{1-3} alkylsulphonylamino, and a saturated heterocyclic group selected from morpholino, thiomorpholino, pyrrolidin-1-yl, piperazin-1-yl, piperazin-4-yl, and piperidino which saturated heterocyclic group may be substituted as hereinbefore defined.

More preferably the substituents on an available ring carbon atom in R^1 are selected independently from halogeno, trifluoromethyl, cyano, nitro, C_{2-3} alkanoyl, C_{1-3} alkoxycarbonyl, C_{1-3} alkylsulphanyl, C_{1-3} alkylsulphinyl, carbamoyl, N - C_{1-3} alkylcarbamoyl, N,N -di(C_{1-3} alkyl)carbamoyl, aminosulphonyl, N - C_{1-3} alkylaminosulphonyl, N,N -di(C_{1-3} alkyl)aminosulphonyl, and a saturated heterocyclic group selected from morpholino, thiomorpholino, pyrrolidin-1-yl, piperazin-1-yl, piperazin-4-yl, and piperidino which saturated heterocyclic group is unsubstituted.

Preferably n is 1.

Preferably m is an integer from 0 to 2, most preferably 2.

Advantageously X^1 represents -O-, -S-, $-NR^6CO-$, $-NR^9SO_2-$ or $-NR^{10}-$ (wherein R^6 , R^9 and R^{10} each independently represents hydrogen, C_{1-2} alkyl or C_{1-2} alkoxyethyl).

98/022

- 7 -

Preferably X^1 represents -O-, -S-, $-NR^6CO-$, $-NR^9SO_2-$ (wherein R^6 and R^9 each independently represents hydrogen or $C_{1-2}alkyl$) or NH.

More preferably X^1 represents -O-, -S-, $-NR^6CO-$ (wherein R^6 represents hydrogen or $C_{1-2}alkyl$) or NH.

5 Particularly X^1 represents -O- or $-NR^6CO-$ (wherein R^6 represents hydrogen or $C_{1-2}alkyl$), more particularly -O- or $-NHCO-$, especially -O-.

Advantageously X^2 represents -O- or NR^{12} (wherein R^{12} represents hydrogen, $C_{1-3}alkyl$ or $C_{1-2}alkoxyethyl$).

10 Advantageously X^3 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{17}CO-$, $-NR^{20}SO_2-$ or $-NR^{21}-$ (wherein R^{17} , R^{20} and R^{21} each independently represents hydrogen, $C_{1-2}alkyl$ or $C_{1-2}alkoxyethyl$).

Preferably X^3 represents -O-, -S-, -SO-, $-SO_2-$ or $-NR^{21}-$ (wherein R^{21} represents hydrogen, $C_{1-2}alkyl$ or $C_{1-2}alkoxyethyl$).

15 More preferably X^3 represents -O- or $-NR^{21}-$ (wherein R^{21} represents hydrogen or $C_{1-2}alkyl$).

Advantageously X^4 and X^5 which may be the same or different each represents -O-, -S-, -SO-, $-SO_2-$ or $-NR^{27}-$ (wherein R^{27} represents hydrogen, $C_{1-3}alkyl$ or $C_{1-2}alkoxyethyl$).

Preferably X^4 and X^5 which may be the same or different each represents -O-, -S- or $-NR^{27}-$ (wherein R^{27} represents hydrogen, $C_{1-2}alkyl$ or $C_{1-2}alkoxyethyl$).

20 More preferably X^4 and X^5 which may be the same or different each represents -O- or -NH-.

Advantageously X^6 represents -O-, -S- or $-NR^{38}-$ (wherein R^{38} represents hydrogen, $C_{1-2}alkyl$ or $C_{1-2}alkoxyethyl$).

25 Preferably X^6 represents -O- or $-NR^{38}-$ (wherein R^{38} represents hydrogen or $C_{1-2}alkyl$).

Advantageously X^7 represents -O-, -S- or $-NR^{43}-$ (wherein R^{43} represents hydrogen, $C_{1-2}alkyl$ or $C_{1-2}alkoxyethyl$).

Preferably X^7 represents -O- or $-NR^{43}-$ (wherein R^{43} represents hydrogen or $C_{1-2}alkyl$).

30 Advantageously X^8 represents -O-, -S- or $-NR^{48}-$ (wherein R^{48} represents hydrogen, $C_{1-2}alkyl$ or $C_{1-2}alkoxyethyl$).

98/022

- 8 -

Preferably X^8 represents -O- or -NR⁴⁸- (wherein R⁴⁸ represents hydrogen or C₁₋₂alkyl).

Advantageously X^9 represents -O-, -S- or -NR⁵³- (wherein R⁵³ represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

5 Preferably X^9 represents -O- or -NR⁵³- (wherein R⁵³ represents hydrogen or C₁₋₂alkyl).

Preferably R²⁸ is pyrrolidinyl, piperazinyl, piperidinyl, morpholino or thiomorpholino (linked preferably via nitrogen) which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃alkoxy, C₁₋₂alkoxyC₁₋₃alkyl and C₁₋₂alkylsulphonylC₁₋₃alkyl.

10 Preferably R²⁹ represents a pyridone group or a 5-6-membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which pyridone group or heterocyclic group may be substituted as hereinbefore defined.

Where R²⁹ is a 5-6-membered aromatic heterocyclic group, it preferably has 1 or 2 heteroatoms, selected from O, N and S, of which more preferably one is N, and may be substituted as hereinbefore defined.

R²⁹ is particularly a pyridone, pyridyl, imidazolyl, thiazolyl, thienyl, triazolyl or pyridazinyl group which group may be substituted as hereinbefore defined, more particularly a pyridone, pyridyl, imidazolyl, thiazolyl or triazolyl group, especially a pyridone, pyridyl, imidazolyl or triazolyl group which group may be substituted as hereinbefore defined.

20 In one embodiment of the invention R²⁹ represents a pyridone, phenyl or 5-6-membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which group may preferably carry up to 2 substituents, more preferably up to one substituent, selected from the group of substituents as hereinbefore defined.

25 In the definition of R²⁹, conveniently substituents are selected from halogeno, C₁₋₄alkyl, C₁₋₄alkoxy and cyano, more conveniently substituents are selected from chloro, fluoro, methyl and ethyl.

Conveniently R² represents hydroxy, halogeno, nitro, trifluoromethyl, C₁₋₃alkyl, cyano, amino or R⁵X¹- [wherein X¹ is as hereinbefore defined and R⁵ is selected from one of the following seventeen groups:

98/022

- 9 -

- 1) C₁₋₅alkyl which may be unsubstituted or substituted with one or more fluorine atoms, or C₂₋₅alkyl which may be unsubstituted or substituted with one or more groups selected from hydroxy and amino;
- 2) C₂₋₃alkylX²COR¹¹ (wherein X² is as hereinbefore defined and R¹¹ represents C₁₋₃alkyl, -NR¹³R¹⁴ or -OR¹⁵ (wherein R¹³, R¹⁴ and R¹⁵ which may be the same or different are each C₁₋₂alkyl or C₁₋₂alkoxyethyl));
- 3) C₂₋₄alkylX³R¹⁶ (wherein X³ is as hereinbefore defined and R¹⁶ represents hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₃alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl and C₁₋₄alkoxy);
- 4) C₂₋₃alkylX⁴C₂₋₃alkylX⁵R²² (wherein X⁴ and X⁵ are as hereinbefore defined and R²² represents hydrogen or C₁₋₃alkyl);
- 5) C₁₋₅alkylR⁵⁴ (wherein R⁵⁴ is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group is linked to C₁₋₅alkyl through a carbon atom and which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl and C₁₋₄alkylsulphonyl(C₁₋₄alkyl) or C₂₋₅alkylR⁵⁵ (wherein R⁵⁵ is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms of which one is N and the other is selected independently from O, S and N, which heterocyclic group is linked to C₂₋₅alkyl through a nitrogen atom and which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl and C₁₋₄alkylsulphonyl(C₁₋₄alkyl));
- 6) C₃₋₄alkenylR⁵⁶ (wherein R⁵⁶ represents R⁵⁴ or R⁵⁵ as defined hereinbefore);
- 7) C₃₋₄alkynylR⁵⁶ (wherein R⁵⁶ represents R⁵⁴ or R⁵⁵ as defined hereinbefore);
- 8) R²⁹ (wherein R²⁹ is as defined hereinbefore);
- 9) C₁₋₅alkylR²⁹ (wherein R²⁹ is as defined hereinbefore);
- 10) C₃₋₅alkenylR²⁹ (wherein R²⁹ is as defined hereinbefore);
- 11) C₃₋₅alkynylR²⁹ (wherein R²⁹ is as defined hereinbefore);
- 12) C₁₋₅alkylX⁶X²⁹ (wherein X⁶ and R²⁹ are as defined hereinbefore);
- 13) C₄₋₅alkenylX⁷R²⁹ (wherein X⁷ and R²⁹ are as defined hereinbefore);

- 14) $C_{4-5}alkynylX^8R^{29}$ (wherein X^8 and R^{29} are as defined hereinbefore);
 15) $C_{2-3}alkylX^9C_{1-2}alkylR^{29}$ (wherein X^9 and R^{29} are as defined hereinbefore);
 16) R^{28} (wherein R^{28} is as defined hereinbefore); and
 17) $C_{2-3}alkylX^9C_{1-2}alkylR^{28}$ (wherein X^9 and R^{28} are as defined hereinbefore)].

5 Advantageously R^2 represents hydroxy, halogeno, nitro, trifluoromethyl, $C_{1-3}alkyl$, cyano, amino or R^5X^1 - [wherein X^1 is as hereinbefore defined and R^5 is selected from one of the following seventeen groups:

- 1) $C_{1-4}alkyl$ which may be unsubstituted or substituted with one or more fluorine atoms, or $C_{2-4}alkyl$ which may be unsubstituted or substituted with 1 or 2 groups selected from hydroxy
 10 and amino;
 2) $C_{2-3}alkylX^2COR^{11}$ (wherein X^2 is as hereinbefore defined and R^{11} represents $-NR^{13}R^{14}$ or $-OR^{15}$ (wherein R^{13} , R^{14} and R^{15} which may be the same or different are each $C_{1-2}alkyl$ or $C_{1-2}alkoxyethyl$));
 3) $C_{2-4}alkylX^3R^{16}$ (wherein X^3 is as hereinbefore defined and R^{16} is a group selected from $C_{1-3}alkyl$, cyclopentyl, cyclohexyl, pyrrolidinyl and piperidinyl which group is linked to X^3
 15 through a carbon atom and which $C_{1-3}alkyl$ group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and $C_{1-2}alkoxy$ and which cyclopentyl, cyclohexyl, pyrrolidinyl or piperidinyl group may carry one substituent selected from oxo, hydroxy, halogeno, $C_{1-2}alkyl$, $C_{1-2}hydroxyalkyl$ and $C_{1-2}alkoxy$);
 20 4) $C_{2-3}alkylX^4C_{2-3}alkylX^5R^{22}$ (wherein X^4 and X^5 are as hereinbefore defined and R^{22} represents hydrogen or $C_{1-3}alkyl$);
 5) $C_{1-4}alkylR^{57}$ (wherein R^{57} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-dithian-2-yl, which group is linked to $C_{1-4}alkyl$ through a carbon atom and which group may carry 1 or 2 substituents
 25 selected from oxo, hydroxy, halogeno, $C_{1-3}alkyl$, $C_{1-3}hydroxyalkyl$, $C_{1-3}alkoxy$, $C_{1-2}alkoxyC_{1-3}alkyl$ and $C_{1-2}alkylsulphonylC_{1-3}alkyl$) or $C_{2-4}alkylR^{58}$ (wherein R^{58} is a group selected from morpholino, thiomorpholino, pyrrolidin-1-yl, piperazin-1-yl and piperidino which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, $C_{1-3}alkyl$, $C_{1-3}hydroxyalkyl$, $C_{1-3}alkoxy$, $C_{1-2}alkoxyC_{1-3}alkyl$ and $C_{1-2}alkylsulphonylC_{1-3}alkyl$);
 30 6) $C_{3-4}alkenylR^{59}$ (wherein R^{59} represents R^{57} or R^{58} as defined hereinbefore);
 7) $C_{3-4}alkynylR^{59}$ (wherein R^{59} represents R^{57} or R^{58} as defined hereinbefore);
 8) R^{29} (wherein R^{29} is as defined hereinbefore);

98/022

- 11 -

9) $C_{1-4}alkylR^{29}$ (wherein R^{29} is as defined hereinbefore);

10) $1-R^{29}prop-1-en-3-yl$ or $1-R^{29}but-2-en-4-yl$ (wherein R^{29} is as defined hereinbefore with the proviso that when R^5 is $1-R^{29}prop-1-en-3-yl$, R^{29} is linked to the alkenyl group via a carbon atom);

5 11) $1-R^{29}prop-1-yn-3-yl$ or $1-R^{29}but-2-yn-4-yl$ (wherein R^{29} is as defined hereinbefore with the proviso that when R^5 is $1-R^{29}prop-1-yn-3-yl$, R^{29} is linked to the alkynyl group via a carbon atom);

12) $C_{1-5}alkylX^6R^{29}$ (wherein X^6 and R^{29} are as defined hereinbefore);

13) $1-(R^{29}X^7)but-2-en-4-yl$ (wherein X^7 and R^{29} are as defined hereinbefore);

10 14) $1-(R^{29}X^8)but-2-yn-4-yl$ (wherein X^8 and R^{29} are as defined hereinbefore);

15) $C_{2-3}alkylX^9C_{1-2}alkylR^{29}$ (wherein X^9 and R^{29} are as defined hereinbefore);

16) R^{28} (wherein R^{28} is as defined hereinbefore); and

17) $C_{2-3}alkylX^9C_{1-2}alkylR^{28}$ (wherein X^9 and R^{28} are as defined hereinbefore)].

15 Preferably R^2 represents hydroxy, halogeno, nitro, trifluoromethyl, $C_{1-3}alkyl$, cyano, amino or R^5X^1 - [wherein X^1 is as hereinbefore defined and R^5 is selected from one of the following fifteen groups:

1) $C_{1-3}alkyl$ which may be unsubstituted or substituted with one or more fluorine atoms, or $C_{2-3}alkyl$ which may be unsubstituted or substituted with 1 or 2 groups selected from hydroxy and amino;

20 2) 2-(3,3-dimethylureido)ethyl, 3-(3,3-dimethylureido)propyl, 2-(3-methylureido)ethyl, 3-(3-methylureido)propyl, 2-ureidoethyl, 3-ureidopropyl, 2-(N,N-dimethylcarbamoxyloxy)ethyl, 3-(N,N-dimethylcarbamoxyloxy)propyl, 2-(N-methylcarbamoxyloxy)ethyl, 3-(N-methylcarbamoxyloxy)propyl, 2-(carbamoxyloxy)ethyl, 3-(carbamoxyloxy)propyl;

25 3) $C_{2-3}alkylX^3R^{16}$ (wherein X^3 is as defined hereinbefore and R^{16} is a group selected from $C_{1-2}alkyl$, cyclopentyl, cyclohexyl, pyrrolidinyl and piperidinyl which group is linked to X^3 through a carbon atom and which $C_{1-2}alkyl$ group may bear 1 or 2 substituents selected from hydroxy, halogeno and $C_{1-2}alkoxy$ and which cyclopentyl, cyclohexyl, pyrrolidinyl or piperidinyl group may carry one substituent selected from oxo, hydroxy, halogeno, $C_{1-2}alkyl$, $C_{1-2}hydroxyalkyl$ and $C_{1-2}alkoxy$);

30 4) $C_{2-3}alkylX^4C_{2-3}alkylX^5R^{22}$ (wherein X^4 and X^5 are as hereinbefore defined and R^{22} represents hydrogen or $C_{1-2}alkyl$);

98/022

- 12 -

- 5) $C_{1-2}alkylR^{57}$ (wherein R^{57} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-dithian-2-yl, which group is linked to $C_{1-2}alkyl$ through a carbon atom and which group may carry one substituent selected from oxo, hydroxy, halogeno, $C_{1-3}alkyl$, $C_{1-3}hydroxyalkyl$, $C_{1-3}alkoxy$, $C_{1-2}alkoxyC_{1-3}alkyl$ and $C_{1-2}alkylsulphonylC_{1-3}alkyl$) or $C_{2-3}alkylR^{58}$ (wherein R^{58} is a group selected from morpholino, thiomorpholino, piperidino, piperazin-1-yl and pyrrolidin-1-yl which group may carry one substituent selected from oxo, hydroxy, halogeno, $C_{1-3}alkyl$, $C_{1-3}hydroxyalkyl$, $C_{1-3}alkoxy$, $C_{1-2}alkoxyC_{1-3}alkyl$ and $C_{1-2}alkylsulphonylC_{1-3}alkyl$);
- 6) R^{29} (wherein R^{29} is as defined hereinbefore);
- 10 7) $C_{1-4}alkylR^{29}$ (wherein R^{29} is as defined hereinbefore);
- 8) 1- R^{29} but-2-en-4-yl (wherein R^{29} is as defined hereinbefore);
- 9) 1- R^{29} but-2-yn-4-yl (wherein R^{29} is as defined hereinbefore);
- 10) $C_{1-5}alkylX^6R^{29}$ (wherein X^6 and R^{29} are as defined hereinbefore);
- 11) 1-($R^{29}X^7$)but-2-en-4-yl (wherein X^7 and R^{29} are as defined hereinbefore);
- 15 12) 1-($R^{29}X^8$)but-2-yn-4-yl (wherein X^8 and R^{29} are as defined hereinbefore);
- 13) ethyl X^9 methyl R^{29} (wherein X^9 and R^{29} are as defined hereinbefore);
- 14) R^{28} (wherein R^{28} is as defined hereinbefore); and
- 15) ethyl X^9 methyl R^{28} (wherein X^9 and R^{28} are as defined hereinbefore)].

- More preferably R^2 represents $C_{1-3}alkyl$, amino or R^5X^1 - [wherein X^1 is as hereinbefore defined and R^5 represents methyl, ethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphinyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoyl ethyl, 2-(N,N-dimethylamino)ethyl, 3-(N,N-dimethylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(methylpiperidino)ethyl, 3-(methylpiperidino)propyl, 2-(ethylpiperidino)ethyl, 3-(ethylpiperidino)propyl, 2-((2-methoxyethyl)piperidino)ethyl, 3-((2-methoxyethyl)piperidino)propyl, 2-((2-methylsulphonyl)ethylpiperidino)ethyl, 3-((2-methylsulphonyl)ethylpiperidino)propyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-(piperidin-3-yl)ethyl, 2-(piperidin-4-yl)ethyl, 3-(piperidin-3-yl)propyl, 3-(piperidin-4-yl)propyl, 2-(methylpiperidin-3-yl)ethyl, 2-(methylpiperidin-4-yl)ethyl, 3-(methylpiperidin-3-yl)propyl, 3-(methylpiperidin-4-yl)propyl, 2-(ethylpiperidin-3-yl)ethyl, 2-(ethylpiperidin-4-yl)ethyl, 3-(ethylpiperidin-3-yl)propyl, 3-(ethylpiperidin-4-yl)propyl, 2-((2-
- 20
- 25
- 30

98/022

- 13 -

methoxyethyl)piperidin-3-yl)ethyl, 2-((2-methoxyethyl)piperidin-4-yl)ethyl, 3-((2-methoxyethyl)piperidin-3-yl)propyl, 3-((2-methoxyethyl)piperidin-4-yl)propyl, 2-((2-methylsulphonyl)ethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonyl)ethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonyl)ethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonyl)ethyl)piperidin-4-yl)propyl, 1-isopropylpiperidin-2-ylmethyl, 1-isopropylpiperidin-3-ylmethyl, 1-isopropylpiperidin-4-ylmethyl, 2-(1-isopropylpiperidin-2-yl)ethyl, 2-(1-isopropylpiperidin-3-yl)ethyl, 2-(1-isopropylpiperidin-4-yl)ethyl, 3-(1-isopropylpiperidin-2-yl)propyl, 3-(1-isopropylpiperidin-3-yl)propyl, 3-(1-isopropylpiperidin-4-yl)propyl, 2-(piperazin-1-yl)ethyl, 3-(piperazin-1-yl)propyl, 2-(pyrrolidin-1-yl)ethyl, 3-(pyrrolidin-1-yl)propyl, (1,3-dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-methylthiazol-4-ylmethyl, 2-acetamidothiazol-4-ylmethyl, 1-methylimidazol-2-ylmethyl, 2-(imidazol-1-yl)ethyl, 2-(2-methylimidazol-1-yl)ethyl, 2-(2-ethylimidazol-1-yl)ethyl, 3-(2-methylimidazol-1-yl)propyl, 3-(2-ethylimidazol-1-yl)propyl, 2-(1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-pyridyl)propyl, 2-(4-pyridyloxy)ethyl, 2-(4-pyridylamino)ethyl, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethyl, 2-thiomorpholinoethyl, 3-thiomorpholinopropyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 3-(methylsulphinyl)propyl, 3-(methylsulphonyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, morpholino, 2-((N-(1-methylimidazol-4-ylsulphonyl)-N-methyl)amino)ethyl, 2-((N-(3-morpholinopropylsulphonyl)-N-methyl)amino)ethyl, 2-((N-methyl-N-4-pyridyl)amino)ethyl or 3-(4-oxidomorpholino)propyl].

In another aspect R^2 represents methoxy, 2-methoxyethoxy, 2-(2-methoxyethoxy)ethoxy, 3-methoxypropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-(tetrahydropyran-4-yloxy)ethoxy, 3-(tetrahydropyran-4-yloxy)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, 2-(1,1-dioxothiomorpholino)ethoxy, 3-(1,1-dioxothiomorpholino)propoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(N-methoxyacetyl-N-methylamino)ethoxy, 3-(N-methoxyacetyl-N-methylamino)propoxy, N-methylpiperidin-3-ylmethoxy, 4-(pyrrolidin-1-yl)but-2-en-yloxy, 2-(2-oxopyrrolidin-1-yl)ethoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-(2-(pyrrolidin-1-yl)ethoxy)ethoxy, 2-(2-

98/022

- 14 -

(4-methylpiperazin-1-yl)ethoxy)ethoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(methylpiperidino)ethoxy, 3-(methylpiperidino)propoxy, 2-(ethylpiperidino)ethoxy, 3-(ethylpiperidino)propoxy, 2-((2-methoxyethyl)piperidino)ethoxy, 3-((2-methoxyethyl)piperidino)propoxy, 2-((2-methylsulphonyl)ethylpiperidino)ethoxy, 3-((2-methylsulphonyl)ethylpiperidino)propoxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-(piperidin-3-yl)ethoxy, 2-(piperidin-4-yl)ethoxy, 3-(piperidin-3-yl)propoxy, 3-(piperidin-4-yl)propoxy, 2-(methylpiperidin-3-yl)ethoxy, 2-(methylpiperidin-4-yl)ethoxy, 3-(methylpiperidin-3-yl)propoxy, 3-(methylpiperidin-4-yl)propoxy, 2-(ethylpiperidin-3-yl)ethoxy, 2-(ethylpiperidin-4-yl)ethoxy, 3-(ethylpiperidin-3-yl)propoxy, 3-(ethylpiperidin-4-yl)propoxy, 2-((2-methoxyethyl)piperidin-3-yl)ethoxy, 2-((2-methoxyethyl)piperidin-4-yl)ethoxy, 3-((2-methoxyethyl)piperidin-3-yl)propoxy, 3-((2-methoxyethyl)piperidin-4-yl)propoxy, 2-((2-methylsulphonyl)ethyl)piperidin-3-yl)ethoxy, 2-((2-methylsulphonyl)ethyl)piperidin-4-yl)ethoxy, 3-((2-methylsulphonyl)ethyl)piperidin-3-yl)propoxy, 3-((2-methylsulphonyl)ethyl)piperidin-4-yl)propoxy, 1-isopropylpiperidin-2-ylmethyl, 1-isopropylpiperidin-3-ylmethyl, 1-isopropylpiperidin-4-ylmethyl, 2-(1-isopropylpiperidin-2-yl)ethyl, 2-(1-isopropylpiperidin-3-yl)ethyl, 2-(1-isopropylpiperidin-4-yl)ethyl, 3-(1-isopropylpiperidin-2-yl)propyl, 3-(1-isopropylpiperidin-3-yl)propyl or 3-(1-isopropylpiperidin-4-yl)propyl.

Where one of the R^2 substituents is R^5X^1 - the substituent R^5X^1 - is preferably at the 6- or 7-position of the quinazoline ring, more preferably at the 7-position of the quinazoline ring.

When one of the R^2 substituents is at the 6-position of the quinazoline ring it is preferably halogeno, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylsulphonyl or $-NR^3R^4$ (wherein R^3 and R^4 are as defined hereinbefore).

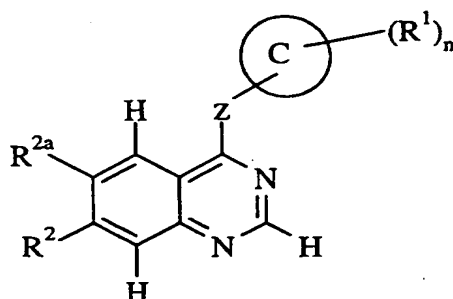
When one of the R^2 substituents is at the 6-position of the quinazoline ring it is more preferably C_{1-3} alkoxy, especially methoxy.

In another aspect of the present invention there is provided the use of compounds of the formula Ia:

30

98/022

- 15 -



(Ia)

[wherein:

ring C, R^1 , R^2 , n and Z are as defined hereinbefore with the proviso that R^2 is not hydrogen; and

R^{2a} represents halogeno, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylthio, $-NR^{3a}R^{4a}$ (wherein R^{3a} and R^{4a} , which may be the same or different, each represents hydrogen or C_{1-3} alkyl), or $R^{5a}(CH_2)_{za}X^{1a}$ (wherein R^{5a} is a 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms,

selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl and C_{1-4} alkoxy, za is an integer from 0 to 4 and X^{1a} represents a direct bond, $-O-$, $-CH_2-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{6a}CO-$, $-CONR^{7a}-$, $-SO_2NR^{8a}-$, $-NR^{9a}SO_2-$ or $-NR^{10a}-$ (wherein R^{6a} , R^{7a} , R^{8a} , R^{9a} and R^{10a} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl));

and salts thereof, and prodrugs thereof for example esters, amides and sulphides, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

Advantageously X^{1a} represents $-O-$, $-S-$, $-NR^{6a}CO-$, $-NR^{9a}SO_2-$ or $-NR^{10a}-$ (wherein R^{6a} , R^{9a} and R^{10a} each independently represents hydrogen, C_{1-2} alkyl or C_{1-2} alkoxyethyl).

Preferably X^{1a} represents $-O-$, $-S-$, $-NR^{6a}CO-$, $-NR^{9a}SO_2-$ (wherein R^{6a} and R^{9a} each independently represents hydrogen or C_{1-2} alkyl) or NH .

More preferably X^{1a} represents $-O-$, $-S-$, $-NR^{6a}CO-$ (wherein R^{6a} represents hydrogen or C_{1-2} alkyl) or NH .

Particularly X^{1a} represents $-O-$ or $-NR^{6a}CO-$ (wherein R^{6a} represents hydrogen or C_{1-2} alkyl), more particularly $-O-$ or $-NHCO-$, especially $-O-$.

Preferably za is an integer from 1 to 3.

98/022

- 16 -

Preferably R^{5a} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, morpholino and thiomorpholino which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-2} alkyl, C_{1-2} hydroxyalkyl and C_{1-2} alkoxy.

Advantageously R^{2a} represents C_{1-3} alkyl, C_{1-3} alkoxy, amino or $R^{5a}(CH_2)_{za}X^{1a}$ (wherein R^{5a} , X^{1a} and za are as defined hereinbefore).

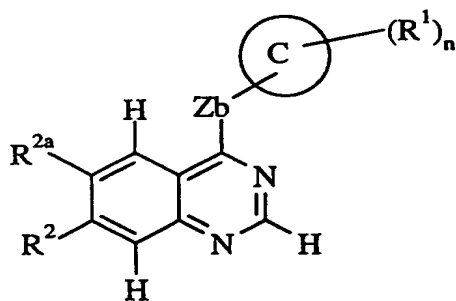
Preferably R^{2a} is methyl, ethyl, methoxy, ethoxy or $R^{5a}(CH_2)_{za}X^{1a}$ (wherein R^{5a} , X^{1a} and za are as defined hereinbefore).

More preferably R^{2a} is methyl, ethyl, methoxy, ethoxy or $R^{5a}(CH_2)_{za}X^{1a}$ (wherein R^{5a} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, morpholino and thiomorpholino which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-2} alkyl, C_{1-2} hydroxyalkyl and C_{1-2} alkoxy, X^{1a} is -O-, -S-, $-NR^{6a}CO-$, $-NR^{9a}SO_2-$ (wherein R^{6a} and R^{9a} each independently represents hydrogen or C_{1-2} alkyl) or NH, and za is an integer from 1 to 3).

Particularly R^{2a} represents methyl, methoxy or $R^{5a}(CH_2)_{za}X^{1a}$ (wherein R^{5a} , X^{1a} and za are as defined hereinbefore).

More particularly R^{2a} represents methoxy.

In a further aspect of the present invention there is provided the use of compounds of the formula Ib:



(Ib)

[wherein:

ring C, R^1 , R^2 , R^{2a} and n are as defined hereinbefore with the proviso that R^2 is not hydrogen; and

Zb is -O- or -S-;

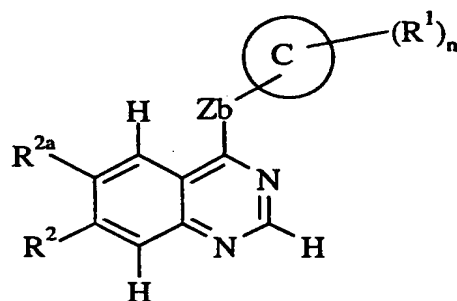
98/022

- 17 -

and salts thereof, and prodrugs thereof for example esters, amides and sulphides, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

Preferably Zb is -O-.

According to another aspect of the present invention there are provided compounds of the formula II:



(II)

[wherein:

ring C, R^1 , R^2 , R^{2a} , Zb and n are as defined hereinbefore with the provisos that R^2 does not have any of the following values:

hydrogen, substituted or unsubstituted C_{1-5} alkyl, halogeno, C_{1-5} alkoxy, phenoxy or phenyl C_{1-5} alkoxy;

and salts thereof, and prodrugs thereof for example esters, amides and sulphides.

Preferred compounds of the present invention include

4-(5-benzylpyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

7-(2-methoxyethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,

4-(5-butylpyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-7-(3-morpholinopropoxy)-4-(5-propylpyrazol-3-yloxy)quinazoline,

4-(5-methoxymethylpyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-7-(3-morpholinopropoxy)-4-(5-(prop-3-en-1yl)pyrazol-3-yloxy)quinazoline,

6-methoxy-7-(3-morpholinopropoxy)-4-(5-(3-pyridyl)pyrazol-3-yloxy)quinazoline,

4-(5-isobutylpyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline and

4-(5-(2-cyclopentylethyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline

98/022

- 18 -

and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters, amides and sulphides.

More preferred compounds of the present invention include

- 4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,
- 4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline,
- 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
- 4-(5-(3-furyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
- 6,7-dimethoxy-4-(5-phenylpyrazol-3-yloxy)quinazoline,
- 6-methoxy-7-(3-morpholinopropoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
- 4-(5-(2-fluorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
- 6-methoxy-7-(3-morpholinopropoxy)-4-(5-(3-nitrophenyl)pyrazol-3-yloxy)quinazoline,
- 6-methoxy-7-(3-morpholinopropoxy)-4-(5-(4-nitrophenyl)pyrazol-3-yloxy)quinazoline,
- 6-methoxy-7-(3-morpholinopropoxy)-4-(5-(4-pyridyl)pyrazol-3-yloxy)quinazoline,
- 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-4-(5-phenylpyrazol-3-yloxy)quinazoline and
- 4-(5-(4-fluorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline
- and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters, amides and sulphides.
- Especially preferred compounds of the present invention include
- 4-(5-(4-chlorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
- 6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
- 6-methoxy-7-(2-methoxyethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline and
- 6-methoxy-7-(2-methoxyethoxy)-4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)quinazoline
- and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters, amides and sulphides.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined' or 'defined hereinbefore' the said group encompasses the first occurring and broadest definition as well as each and all of the preferred definitions for that group.

In this specification unless stated otherwise the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are

98/022

- 19 -

specific for the straight chain version only. An analogous convention applies to other generic terms. Unless otherwise stated the term "alkyl" advantageously refers to chains with 1-6 carbon atoms, preferably 1-4 carbon atoms. The term "alkoxy" as used herein, unless stated otherwise includes "alkyl"-O- groups in which "alkyl" is as hereinbefore defined. The term "aryl" as used herein unless stated otherwise includes reference to a C₆₋₁₀ aryl group which may, if desired, carry one or more substituents selected from halogeno, alkyl, alkoxy, nitro, trifluoromethyl and cyano, (wherein alkyl and alkoxy are as hereinbefore defined). The term "aryloxy" as used herein unless otherwise stated includes "aryl"-O-groups in which "aryl" is as hereinbefore defined. The term "sulphonyloxy" as used herein refers to alkylsulphonyloxy and arylsulphonyloxy groups in which "alkyl" and "aryl" are as hereinbefore defined. The term "alkanoyl" as used herein unless otherwise stated includes formyl and alkylC=O groups in which "alkyl" is as defined hereinbefore, for example C₂alkanoyl is ethanoyl and refers to CH₃C=O, C₁alkanoyl is formyl and refers to CHO. In this specification unless stated otherwise the term "alkenyl" includes both straight and branched chain alkenyl groups but references to individual alkenyl groups such as 2-butenyl are specific for the straight chain version only. Unless otherwise stated the term "alkenyl" advantageously refers to chains with 2-5 carbon atoms, preferably 3-4 carbon atoms. In this specification unless stated otherwise the term "alkynyl" includes both straight and branched chain alkynyl groups but references to individual alkynyl groups such as 2-butylnyl are specific for the straight chain version only. Unless otherwise stated the term "alkynyl" advantageously refers to chains with 2-5 carbon atoms, preferably 3-4 carbon atoms.

Within the present invention it is to be understood that a compound of the formula I or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which inhibits VEGF receptor tyrosine kinase activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It will be appreciated that compounds of the formula I or a salt thereof may possess an asymmetric carbon atom. Such an asymmetric carbon atom is also involved in the

98/022

- 20 -

tautomerism described above, and it is to be understood that the present invention encompasses any chiral form (including both pure enantiomers and racemic mixtures) as well as any tautomeric form which inhibits VEGF receptor tyrosine kinase activity, and is not to be limited merely to any one tautomeric form or chiral form utilised within the formulae drawings. It is to be understood that the invention encompasses all optical and diastereomers which inhibit VEGF receptor tyrosine kinase activity.

It is also to be understood that certain compounds of the formula I and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which inhibit VEGF receptor tyrosine kinase activity.

For the avoidance of any doubt, it is to be understood that when X^1 is, for example, a group of formula $-NR^6CO-$, it is the nitrogen atom bearing the R^6 group which is attached to the quinazoline ring and the carbonyl (CO) group is attached to R^5 , whereas when X^1 is, for example, a group of formula $-CONR^7-$, it is the carbonyl group which is attached to the quinazoline ring and the nitrogen atom bearing the R^7 group is attached to R^5 . A similar convention applies to the other two atom X^1 linking groups such as $-NR^9SO_2-$ and $-SO_2NR^8-$. When X^1 is $-NR^{10}-$ it is the nitrogen atom bearing the R^{10} group which is linked to the quinazoline ring and to R^5 . An analogous convention applies to other groups. It is further to be understood that when X^1 represents $-NR^{10}-$ and R^{10} is $C_{1-3}alkoxyC_{2-3}alkyl$ it is the $C_{2-3}alkyl$ moiety which is linked to the nitrogen atom of X^1 and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that in a compound of the formula I when R^5 is, for example, a group of formula $C_{1-5}alkylX^9C_{1-5}alkylR^{29}$, it is the terminal $C_{1-5}alkyl$ moiety which is linked to X^1 , similarly when R^5 is, for example, a group of formula $C_{2-5}alkenylR^{28}$ it is the $C_{2-5}alkenyl$ moiety which is linked to X^1 and an analogous convention applies to other groups. When R^5 is a group 1- R^{29} prop-1-en-3-yl it is the first carbon to which the group R^{29} is attached and it is the third carbon which is linked to X^1 and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when R^{29} carries a $C_{1-4}aminoalkyl$ substituent it is the $C_{1-4}alkyl$ moiety which is attached to R^{29} whereas when R^{29} carries a $C_{1-4}alkylamino$ substituent it is the amino moiety which is attached to R^{29} and an analogous convention applies to other groups.

98/022

- 21 -

For the avoidance of any doubt, it is to be understood that when R^{28} carries a C_{1-4} alkoxy C_{1-4} alkyl substituent it is the C_{1-4} alkyl moiety which is attached to R^{28} and an analogous convention applies to other groups.

The present invention relates to the compounds of formula I as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula I as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. In addition where the compounds of formula I are sufficiently acidic, pharmaceutically acceptable salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

A compound of the formula I, or salt thereof, and other compounds of the invention (as hereinafter defined) may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes include, for example, those illustrated in European Patent Applications Publication Nos. 0520722, 0566226, 0602851 and 0635498. Such processes also include, for example, solid phase synthesis. Such processes, are provided as a further feature of the invention and are as described hereinafter. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

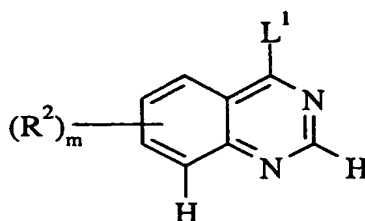
Thus, the following processes (a) to (f) and (i) to (vi) constitute further features of the present invention.

98/022

- 22 -

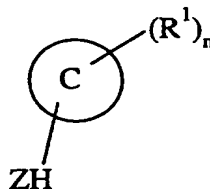
Synthesis of Compounds of Formula I

(a) Compounds of the formula I and salts thereof may be prepared by the reaction of a compound of the formula III:



(III)

(wherein R^2 and m are as defined hereinbefore and L^1 is a displaceable moiety), with a compound of the formula IV:



(IV)

(wherein ring C, R^1 , Z and n are as defined hereinbefore) to obtain compounds of the formula I and salts thereof. A convenient displaceable moiety L^1 is, for example, a halogeno, alkoxy (preferably C_{1-4} alkoxy), aryloxy, alkylsulphanyl, arylsulphanyl, alkoxyalkylsulphanyl or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, methylsulphanyl, 2-methoxyethylsulphanyl, methanesulphonyloxy or toluene-4-sulphonyloxy group.

The reaction is advantageously effected in the presence of a base. Such a base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, *N*-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, tetramethylguanidine or for example, an alkali metal or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide. Alternatively such a base is, for example, an alkali metal hydride, for example sodium hydride, or an alkali metal

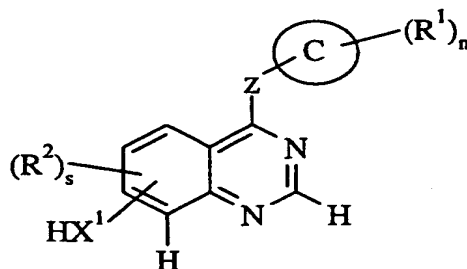
98/022

- 23 -

or alkaline earth metal amide, for example sodium amide, sodium bis(trimethylsilyl)amide, potassium amide or potassium bis(trimethylsilyl)amide. The reaction is preferably effected in the presence of an inert solvent or diluent, for example an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic hydrocarbon solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethyl sulphoxide. The reaction is conveniently effected at a temperature in the range, for example, 10 to 150°C, preferably in the range 20 to 90°C.

When it is desired to obtain the acid salt, the free base may be treated with an acid such as a hydrogen halide, for example hydrogen chloride, sulphuric acid, a sulphonic acid, for example methane sulphonic acid, or a carboxylic acid, for example acetic or citric acid, using a conventional procedure.

(b) Production of those compounds of formula I and salts thereof wherein at least one R^2 is R^5X^1 wherein R^5 is as defined hereinbefore and X^1 is -O-, -S-, -OCO- or -NR¹⁰- (wherein R¹⁰ independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) can be achieved by the reaction, conveniently in the presence of a base (as defined hereinbefore in process (a)) of a compound of the formula V:



(V)

(wherein ring C, Z, R¹, R² and n are as hereinbefore defined and X¹ is as hereinbefore defined in this section and s is an integer from 0 to 2) with a compound of formula VI:



(VI)

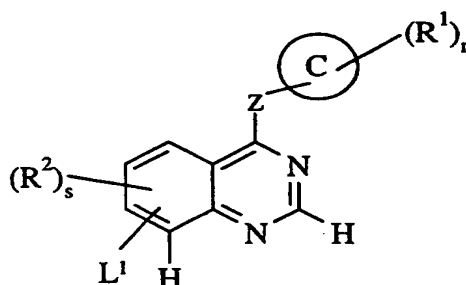
(wherein R⁵ and L¹ are as hereinbefore defined), L¹ is a displaceable moiety for example a halogeno or sulphonyloxy group such as a bromo, methanesulphonyloxy or toluene-4-

98/022

- 24 -

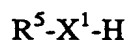
sulphonyloxy group, or L^1 may be generated in situ from an alcohol under standard Mitsunobu conditions ("Organic Reactions", John Wiley & Sons Inc, 1992, vol 42, chapter 2, David L Hughes). The reaction is preferably effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 50°C.

(c) Compounds of the formula I and salts thereof wherein at least one R^2 is R^5X^1 wherein R^5 is as defined hereinbefore and X^1 is -O-, -S-, -OCO- or -NR¹⁰- (wherein R^{10} represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) may be prepared by the reaction of a compound of the formula VII:



(VII)

with a compound of the formula VIII:



(VIII)

(wherein L^1 , R^1 , R^2 , R^5 , ring C, Z, n and s are all as hereinbefore defined and X^1 is as hereinbefore defined in this section). The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 100°C.

(d) Compounds of the formula I and salts thereof wherein at least one R^2 is R^5X^1 wherein X^1 is as defined hereinbefore and R^5 is C₁₋₃alkylR⁶⁰, wherein R^{60} is selected from one of the following six groups:

98/022

- 25 -

1) $X^{10}C_{1-3}alkyl$ (wherein X^{10} represents $-O-$, $-S-$, $-SO_2-$, $-NR^{61}CO-$ or $-NR^{62}SO_2-$ (wherein R^{61} and R^{62} which may be the same or different are each hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_2-3alkyl$);

2) $NR^{63}R^{64}$ (wherein R^{63} and R^{64} which may be the same or different are each hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$);

3) $X^{11}C_{1-5}alkylX^5R^{22}$ (wherein X^{11} represents $-O-$, $-S-$, $-SO_2-$, $-NR^{65}CO-$, $-NR^{66}SO_2-$ or $-NR^{67}-$ (wherein R^{65} , R^{66} , and R^{67} which may be the same or different are each hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$) and X^5 and R^{22} are as defined hereinbefore);

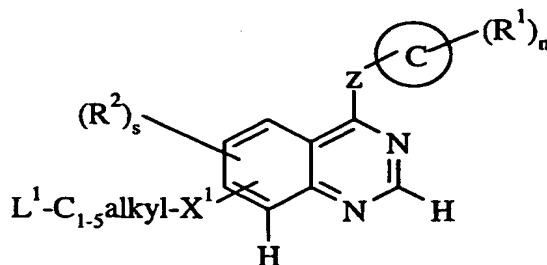
4) R^{28} (wherein R^{28} is as defined hereinbefore);

5) $X^{12}R^{29}$ (wherein X^{12} represents $-O-$, $-S-$, $-SO_2-$, $-NR^{68}CO-$, $-NR^{69}SO_2-$, or $-NR^{70}-$ (wherein R^{68} , R^{69} , and R^{70} which may be the same or different are each hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$) and R^{29} is as defined hereinbefore); and

6) $X^{13}C_{1-5}alkylR^{29}$ (wherein X^{13} represents $-O-$, $-S-$, $-SO_2-$, $-NR^{71}CO-$, $-NR^{72}SO_2-$ or $-NR^{73}-$ (wherein R^{71} , R^{72} and R^{73} each independently represents hydrogen, $C_{1-3}alkyl$ or

$C_{1-3}alkoxyC_{2-3}alkyl$) and R^{29} is as defined hereinbefore);

may be prepared by reacting a compound of the formula IX:



(IX)

(wherein L^1 , X^1 , R^1 , R^2 , ring C, Z, n and s are as hereinbefore defined) with a compound of the formula X:



(X)

(wherein R^{60} is as defined hereinbefore) to give a compound of the formula I or salt thereof.

The reaction may conveniently be effected in the presence of a base (as defined hereinbefore)

98/022

- 26 -

in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), and at a temperature in the range, for example 0 to 150°C, conveniently at about 50°C.

Process (a) is preferred over processes (b), (c) and (d).

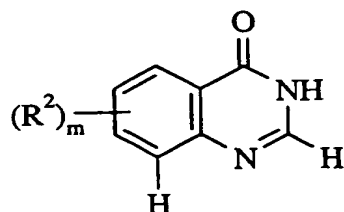
- 5 (e) The production of those compounds of the formula I and salts thereof wherein one or more of the substituents $(R^2)_m$ is represented by $-NR^{74}R^{75}$, where one (and the other is hydrogen) or both of R^{74} and R^{75} are C_{1-3} alkyl, may be effected by the reaction of compounds of formula I wherein the substituent $(R^2)_m$ is an amino group and an alkylating agent, preferably in the presence of a base as defined hereinbefore. Such alkylating agents are
- 10 C_{1-3} alkyl moieties bearing a displaceable moiety as defined hereinbefore such as C_{1-3} alkyl halides for example C_{1-3} alkyl chloride, bromide or iodide. The reaction is preferably effected in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)) and at a temperature in the range, for example, 10 to 100°C, conveniently at about ambient temperature. The production of compounds of formula I and salts thereof wherein one or
- 15 more of the substituents R^2 is an amino group may be effected by the reduction of a corresponding compound of formula I wherein the substituent(s) at the corresponding position(s) of the quinazoline group is/are a nitro group(s). The reduction may conveniently be effected as described in process (i) hereinafter. The production of a compound of formula I and salts thereof wherein the substituent(s) at the corresponding position(s) of the quinazoline
- 20 group is/are a nitro group(s) may be effected by the processes described hereinbefore and hereinafter in processes (a-d) and (i-v) using a compound selected from the compounds of the formulae (I-XXII) in which the substituent(s) at the corresponding position(s) of the quinazoline group is/are a nitro group(s).
- (f) Compounds of the formula I and salts thereof wherein X^1 is $-SO-$ or $-SO_2-$ may be
- 25 prepared by oxidation from the corresponding compound in which X^1 is $-S-$ or $-SO-$ (when X^1 is $-SO_2-$ is required in the final product). Conventional oxidation conditions and reagents for such reactions are well known to the skilled chemist.

Synthesis of Intermediates

- (i) The compounds of formula III and salts thereof in which L^1 is halogeno may for
- 30 example be prepared by halogenating a compound of the formula XI:

98/022

- 27 -



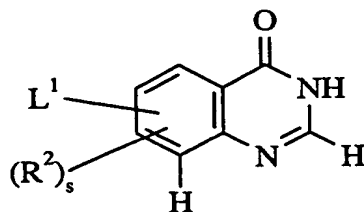
(XI)

wherein R^2 and m are as hereinbefore defined).

Convenient halogenating agents include inorganic acid halides, for example thionyl chloride, phosphorus(III)chloride, phosphorus(V)oxychloride and phosphorus(V)chloride.

The halogenation reaction may be effected in the presence of an inert solvent or diluent such as for example a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, or an aromatic hydrocarbon solvent such as benzene or toluene, or the reaction may be effected without the presence of a solvent. The reaction is conveniently effected at a temperature in the range, for example 10 to 150°C, preferably in the range 40 to 100°C.

The compounds of formula XI and salts thereof may, for example, be prepared by reacting a compound of the formula XII:



(XII)

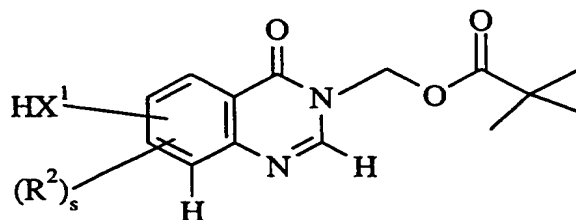
(wherein R^2 , s and L^1 are as hereinbefore defined) with a compound of the formula VIII as hereinbefore defined. The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 100°C.

Compounds of formula XI and salts thereof wherein at least one R^2 is R^5X^1 and wherein X^1 is -O-, -S-, -SO-, -SO₂-, -CO-, -CONR⁷-, -SO₂NR⁸- or -NR¹⁰- (wherein R^7 , R^8 and

98/022

- 28 -

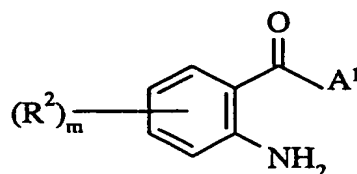
R^{10} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl), may for example also be prepared by the reaction of a compound of the formula XIII:



(XIII)

(wherein R^2 and s are as hereinbefore defined and X^1 is as hereinbefore defined in this section) with a compound of the formula VI as hereinbefore defined. The reaction may for example be effected as described for process (b) hereinbefore. The pivaloyloxymethyl group can then be cleaved by reacting the product with a base such as, for example, aqueous ammonia, triethylamine in water, an alkali metal or alkaline earth metal hydroxide or alkoxide, preferably aqueous ammonia, aqueous sodium hydroxide or aqueous potassium hydroxide, in a polar protic solvent such as an alcohol, for example methanol or ethanol. The reaction is conveniently effected at a temperature in the range 20 to 100°C, preferably in the range 20 to 50°C.

The compounds of formula XI and salts thereof may also be prepared by cyclising a compound of the formula XIV:



(XIV)

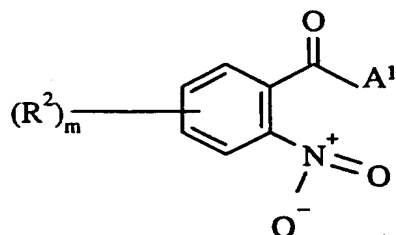
(wherein R^2 and m , are as hereinbefore defined, and A^1 is an hydroxy, alkoxy (preferably C_{1-4} alkoxy) or amino group) whereby to form a compound of formula XI or salt thereof. The cyclisation may be effected by reacting a compound of the formula XIV, where A^1 is an hydroxy or alkoxy group, with formamide or an equivalent thereof effective to cause cyclisation whereby a compound of formula XI or salt thereof is obtained, such as [3-

98/022

- 29 -

(dimethylamino)-2-azaprop-2-enylidene]dimethylammonium chloride. The cyclisation is conveniently effected in the presence of formamide as solvent or in the presence of an inert solvent or diluent such as an ether for example 1,4-dioxan. The cyclisation is conveniently effected at an elevated temperature, preferably in the range 80 to 200°C. The compounds of formula XI may also be prepared by cyclising a compound of the formula XIV, where A¹ is an amino group, with formic acid or an equivalent thereof effective to cause cyclisation whereby a compound of formula XI or salt thereof is obtained. Equivalents of formic acid effective to cause cyclisation include for example a tri-C₁₋₄alkoxymethane, for example triethoxymethane and trimethoxymethane. The cyclisation is conveniently effected in the presence of a catalytic amount of an anhydrous acid, such as a sulphonic acid for example p-toluenesulphonic acid, and in the presence of an inert solvent or diluent such as for example a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, an ether such as diethyl ether or tetrahydrofuran, or an aromatic hydrocarbon solvent such as toluene. The cyclisation is conveniently effected at a temperature in the range, for example 10 to 100°C, preferably in the range 20 to 50°C.

Compounds of formula XIV and salts thereof may for example be prepared by the reduction of the nitro group in a compound of the formula XV:



(XV)

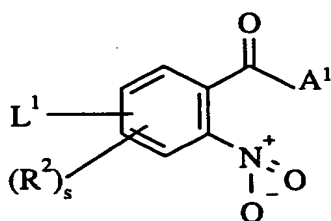
(wherein R², m and A¹ are as hereinbefore defined) to yield a compound of formula XIV as hereinbefore defined. The reduction of the nitro group may conveniently be effected by any of the procedures known for such a transformation. The reduction may be carried out, for example, by stirring a solution of the nitro compound under hydrogen at 1 to 4 atmospheres pressure in the presence of an inert solvent or diluent as defined hereinbefore in the presence of a metal effective to catalyse hydrogenation reactions such as palladium or platinum. A

98/022

- 30 -

further reducing agent is, for example, an activated metal such as activated iron (produced for example by washing iron powder with a dilute solution of an acid such as hydrochloric acid). Thus, for example, the reduction may be effected by heating the nitro compound under hydrogen at 2 atmospheres pressure in the presence of the activated metal and a solvent or
5 diluent such as a mixture of water and alcohol, for example methanol or ethanol, at a temperature in the range, for example 50 to 150°C, conveniently at about 70°C.

Compounds of the formula XV and salts thereof may for example be prepared by the reaction of a compound of the formula XVI:

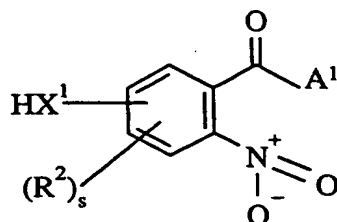


10

(XVI)

(wherein R^2 , s , L^1 and A^1 are as hereinbefore defined) with a compound of the formula VIII as hereinbefore defined to give a compound of the formula XV. The reaction of the compounds
15 of formulae XVI and VIII is conveniently effected under conditions as described for process (c) hereinbefore.

Compounds of formula XV and salts thereof wherein at least one R^2 is R^5X^1 and wherein X^1 is $-\text{O}-$, $-\text{S}-$, $-\text{SO}_2-$, $-\text{CO}-$, $-\text{CONR}^7-$, $-\text{SO}_2\text{NR}^8-$ or $-\text{NR}^{10}-$ (wherein R^7 , R^8 and R^{10} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl), may for example
20 also be prepared by the reaction of a compound of the formula XVII:



(XVII)

98/022

- 31 -

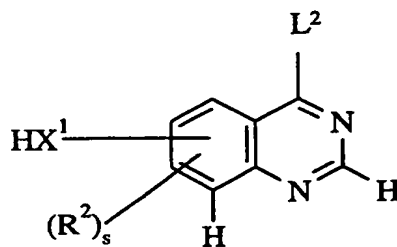
(wherein R^2 , s and A^1 are as hereinbefore defined and X^1 is as hereinbefore defined in this section) with a compound of the formula VI as hereinbefore defined to yield a compound of formula XV as hereinbefore defined. The reaction of the compounds of formulae XVII and VI is conveniently effected under conditions as described for process (b) hereinbefore.

5 The compounds of formula III and salts thereof wherein at least one R^2 is R^5X^1 and wherein X^1 is $-CH_2-$ may be prepared for example as described above from a compound of the formula XV (in which R^2 is $-CH_3$) or XIII (in which HX^1- is $-CH_3$), by radical bromination or chlorination to give a $-CH_2Br$ or $-CH_2Cl$ group which may then be reacted with a compound of the formula R^5-H under standard conditions for such substitution reactions.

10 The compounds of formula III and salts thereof wherein at least one R^2 is R^5X^1 and wherein X^1 is a direct bond may be prepared for example as described above from a compound of the formula XI, wherein the R^5 group is already present in the intermediate compounds (for example in a compound of the formula XV) used to prepare the compound of formula XI.

15 The compounds of formula III and salts thereof wherein at least one R^2 is R^5X^1 and wherein X^1 is $-NR^6CO-$ or $-NR^9SO_2-$ may be prepared for example from a compound of the formula XIII in which HX^1- is an $-NHR^6-$ or $-NHR^9-$ group (prepared for example from an amino group (later functionalised if necessary) by reduction of a nitro group) which is reacted with an acid chloride or sulfonyl chloride compound of the formula R^5COCl or R^5SO_2Cl .

20 The compounds of formula III and salts thereof wherein at least one R^2 is R^5X^1 and wherein X^1 is $-O-$, $-S-$, $-SO_2-$, $-OCO-$, $-CONR^7-$, $-SO_2NR^8-$ or $-NR^{10}-$ (wherein R^7 , R^8 and R^{10} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl), may also be prepared for example by reacting a compound of the formula XVIII:



30

(XVIII)

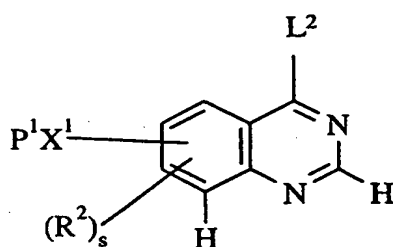
98/022

- 32 -

(wherein R^2 and s are as hereinbefore defined, X^1 is as hereinbefore defined in this section and L^2 represents a displaceable protecting moiety) with a compound of the formula VI as hereinbefore defined, whereby to obtain a compound of formula III in which L^1 is represented by L^2 .

- 5 A compound of formula XVIII is conveniently used in which L^2 represents a phenoxy group which may if desired carry up to 5 substituents, preferably up to 2 substituents, selected from halogeno, nitro and cyano. The reaction may be conveniently effected under conditions as described for process (b) hereinbefore.

10 The compounds of formula XVIII and salts thereof may for example be prepared by deprotecting a compound of the formula XIX:



(XIX)

- 15 (wherein R^2 , s and L^2 are as hereinbefore defined, P^1 is a protecting group and X^1 is as hereinbefore defined in the section describing compounds of the formula XVIII). The choice of protecting group P^1 is within the standard knowledge of an organic chemist, for example those included in standard texts such as "Protective Groups in Organic Synthesis" T.W. Greene and R.G.M. Wuts, 2nd Ed. Wiley 1991, including N-sulphonyl derivatives (for example, p-toluenesulphonyl), carbamates (for example, t-butyl carbonyl), N-alkyl derivatives (for example, 2-chloroethyl, benzyl) and amino acetal derivatives (for example benzyloxymethyl). The removal of such a protecting group may be effected by any of the procedures known for such a transformation, including those reaction conditions indicated in
- 25 standard texts such as that indicated hereinbefore, or by a related procedure. Deprotection may be effected by techniques well known in the literature, for example where P^1 represents a benzyl group deprotection may be effected by hydrogenolysis or by treatment with trifluoroacetic acid.

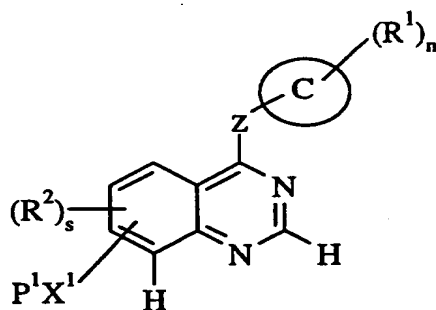
98/022

- 33 -

One compound of formula III may if desired be converted into another compound of formula III in which the moiety L^1 is different. Thus for example a compound of formula III in which L^1 is other than halogeno, for example optionally substituted phenoxy, may be converted to a compound of formula III in which L^1 is halogeno by hydrolysis of a compound of formula III (in which L^1 is other than halogeno) to yield a compound of formula XI as hereinbefore defined, followed by introduction of halide to the compound of formula XI, thus obtained as hereinbefore defined, to yield a compound of formula III in which L^1 represents halogen.

(ii) Compounds of formula IV and salts thereof in which ring C is pyrazolyl may be prepared for example by reacting hydrazine with either a compound of the formula $R^2-C\equiv C-CO_2-C_{1-4}alkyl$, (Al-Jallo et al, J. Het. Chem. 1976, 13, 455), or a compound of the formula $R^2-C(O)-CH_2-C(O)-O-C_{1-4}alkyl$. In both cases the reaction may be effected by heating the keto-ester compound in an inert diluent or solvent such as methanol, ethanol, isopropanol, isopentanol (preferably ethanol) in the presence of hydrazine hydrate. The reaction is effected at a temperature in a range 25-150°C preferably 50-100°C.

(iii) Compounds of formula V as hereinbefore defined and salts thereof may be made by deprotecting the compound of formula XX:



(XX)

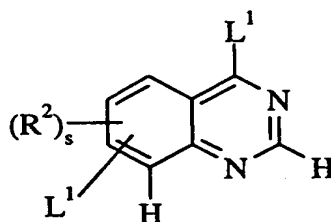
(wherein ring C, Z, R^1 , R^2 , P^1 , n and s are as hereinbefore defined and X^1 is as hereinbefore defined in the section describing compounds of the formula V) by a process for example as described in (i) above.

Compounds of the formula XX and salts thereof may be made by reacting compounds of the formulae XIX and IV as hereinbefore defined, under the conditions described in (a) hereinbefore, to give a compound of the formula XX or salt thereof.

98/022

- 34 -

(iv) Compounds of the formula VII and salts thereof may be made by reacting a compound of the formula XXI:



(XXI)

10 (wherein R^2 , s and each L^1 are as hereinbefore defined and the L^1 in the 4-position and the other L^1 in a further position on the quinazoline ring may be the same or different) with a compound of the formula IV as hereinbefore defined, the reaction for example being effected by a process as described in (a) above.

(v) Compounds of formula IX as defined hereinbefore and salts thereof may for
15 example be made by the reaction of compounds of formula V as defined hereinbefore with compounds of the formula XXII:



20 (wherein L^1 is as hereinbefore defined) to give compounds of formula IX or salts thereof. The reaction may be effected for example by a process as described in (b) above.

(vi) Intermediate compounds wherein X^1 is $-SO-$ or $-SO_2-$ may be prepared by oxidation from the corresponding compound in which X^1 is $-S-$ or $-SO-$ (when X^1 is $-SO_2-$ is required in the final product). Conventional oxidation conditions and reagents for such reactions are well
25 known to the skilled chemist.

When a pharmaceutically acceptable salt of a compound of the formula I is required, it may be obtained, for example, by reaction of said compound with, for example, an acid using a conventional procedure, the acid having a pharmaceutically acceptable anion.

Many of the intermediates defined herein, for example, those of the formulae V, VII,
30 IX and XX are novel and these are provided as a further feature of the invention. The preparation of these compounds is as described herein and/or is by methods well known to persons skilled in the art of organic chemistry.

98/022

- 35 -

The identification of compounds which potentially inhibit the tyrosine kinase activity associated with VEGF receptors such as Flt and/or KDR and which inhibit angiogenesis and/or increased vascular permeability is desirable and is the subject of the present invention. These properties may be assessed, for example, using one or more of the procedures set out below:

(a) In Vitro Receptor Tyrosine Kinase Inhibition Test

This assay determines the ability of a test compound to inhibit tyrosine kinase activity. DNA encoding VEGF, FGF or EGF receptor cytoplasmic domains may be obtained by total gene synthesis (Edwards M, International Biotechnology Lab 5(3), 19-25, 1987) or by cloning. These may then be expressed in a suitable expression system to obtain polypeptide with tyrosine kinase activity. For example VEGF, FGF and EGF receptor cytoplasmic domains, which were obtained by expression of recombinant protein in insect cells, were found to display intrinsic tyrosine kinase activity. In the case of the VEGF receptor Flt (Genbank accession number X51602), a 1.7kb DNA fragment encoding most of the cytoplasmic domain, commencing with methionine 783 and including the termination codon, described by Shibuya et al (Oncogene, 1990, 5: 519-524), was isolated from cDNA and cloned into a baculovirus transplacement vector (for example pAcYM1 (see The Baculovirus Expression System: A Laboratory Guide, L.A. King and R. D. Possee, Chapman and Hall, 1992) or pAc360 or pBlueBacHis (available from Invitrogen Corporation)). This recombinant construct was co-transfected into insect cells (for example *Spodoptera frugiperda* 21(Sf21)) with viral DNA (eg Pharmingen BaculoGold) to prepare recombinant baculovirus. (Details of the methods for the assembly of recombinant DNA molecules and the preparation and use of recombinant baculovirus can be found in standard texts for example Sambrook et al, 1989, Molecular cloning - A Laboratory Manual, 2nd edition, Cold Spring Harbour Laboratory Press and O'Reilly et al, 1992, Baculovirus Expression Vectors - A Laboratory Manual, W. H. Freeman and Co, New York). For other tyrosine kinases for use in assays, cytoplasmic fragments starting from methionine 806 (KDR, Genbank accession number L04947), methionine 668 (EGF receptor, Genbank accession number X00588) and methionine 399 (FGF R1 receptor, Genbank accession number X51803) may be cloned and expressed in a similar manner.

For expression of cFlt tyrosine kinase activity, Sf21 cells were infected with plaque-pure cFlt recombinant virus at a multiplicity of infection of 3 and harvested 48 hours

98/022

- 36 -

later. Harvested cells were washed with ice cold phosphate buffered saline solution (PBS) (10mM sodium phosphate pH7.4, 138mM sodium chloride, 2.7mM potassium chloride) then resuspended in ice cold HNTG/PMSF (20mM Hepes pH7.5, 150mM sodium chloride, 10% v/v glycerol, 1% v/v Triton X100, 1.5mM magnesium chloride, 1mM ethylene glycol-

- 5 bis(β-aminoethyl ether) N,N,N',N'-tetraacetic acid (EGTA), 1mM PMSF (phenylmethylsulphonyl fluoride); the PMSF is added just before use from a freshly-prepared 100mM solution in methanol) using 1ml HNTG/PMSF per 10 million cells. The suspension was centrifuged for 10 minutes at 13,000 rpm at 4°C, the supernatant (enzyme stock) was removed and stored in aliquots at -70°C. Each new batch of stock enzyme was titrated in the
- 10 assay by dilution with enzyme diluent (100mM Hepes pH 7.4, 0.2mM sodium orthovanadate, 0.1% v/v Triton X100, 0.2mM dithiothreitol). For a typical batch, stock enzyme is diluted 1 in 2000 with enzyme diluent and 50μl of dilute enzyme is used for each assay well.

- A stock of substrate solution was prepared from a random copolymer containing tyrosine, for example Poly (Glu, Ala, Tyr) 6:3:1 (Sigma P3899), stored as 1 mg/ml stock in
- 15 PBS at -20°C and diluted 1 in 500 with PBS for plate coating.

On the day before the assay 100μl of diluted substrate solution was dispensed into all wells of assay plates (Nunc maxisorp 96-well immunoplates) which were sealed and left overnight at 4°C.

- On the day of the assay the substrate solution was discarded and the assay plate
- 20 wells were washed once with PBST (PBS containing 0.05% v/v Tween 20) and once with 50mM Hepes pH7.4.

- Test compounds were diluted with 10% dimethylsulphoxide (DMSO) and 25μl of diluted compound was transferred to wells in the washed assay plates. "Total" control wells contained 10% DMSO instead of compound. Twenty five microlitres of 40mM
- 25 manganese(II)chloride containing 8μM adenosine-5'-triphosphate (ATP) was added to all test wells except "blank" control wells which contained manganese(II)chloride without ATP. To start the reactions 50μl of freshly diluted enzyme was added to each well and the plates were incubated at room temperature for 20 minutes. The liquid was then discarded and the wells were washed twice with PBST. One hundred microlitres of mouse IgG anti-phosphotyrosine
- 30 antibody (Upstate Biotechnology Inc. product 05-321), diluted 1 in 6000 with PBST containing 0.5% w/v bovine serum albumin (BSA), was added to each well and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the

98/022

- 37 -

wells twice with PBST. One hundred microlitres of horse radish peroxidase (HRP)-linked sheep anti-mouse Ig antibody (Amersham product NXA 931), diluted 1 in 500 with PBST containing 0.5% w/v BSA, was added and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the wells twice with PBST. One hundred microlitres of 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) solution, freshly prepared using one 50mg ABTS tablet (Boehringer 1204 521) in 50ml freshly prepared 50mM phosphate-citrate buffer pH5.0 + 0.03% sodium perborate (made with 1 phosphate citrate buffer with sodium perborate (PCSB) capsule (Sigma P4922) per 100ml distilled water), was added to each well. Plates were then incubated for 20-60 minutes at room temperature until the optical density value of the "total" control wells, measured at 405nm using a plate reading spectrophotometer, was approximately 1.0. "Blank" (no ATP) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity.

(b) In Vitro HUVEC Proliferation Assay

This assay determines the ability of a test compound to inhibit the growth factor-stimulated proliferation of human umbilical vein endothelial cells (HUVEC).

HUVEC cells were isolated in MCDB 131 (Gibco BRL) + 7.5% v/v foetal calf serum (FCS) and were plated out (at passage 2 to 8), in MCDB 131 + 2% v/v FCS + 3µg/ml heparin + 1µg/ml hydrocortisone, at a concentration of 1000 cells/well in 96 well plates. After a minimum of 4 hours they were dosed with the appropriate growth factor (i.e. VEGF 3ng/ml, EGF 3ng/ml or b-FGF 0.3ng/ml) and compound. The cultures were then incubated for 4 days at 37°C with 7.5% CO₂. On day 4 the cultures were pulsed with 1µCi/well of tritiated-thymidine (Amersham product TRA 61) and incubated for 4 hours. The cells were harvested using a 96-well plate harvester (Tomtek) and then assayed for incorporation of tritium with a Beta plate counter. Incorporation of radioactivity into cells, expressed as cpm, was used to measure inhibition of growth factor-stimulated cell proliferation by compounds.

(c) In Vivo Rat Uterine Oedema Assay

This test measures the capacity of compounds to reduce the acute increase in uterine weight in rats which occurs in the first 4-6 hours following oestrogen stimulation. This early increase in uterine weight has long been known to be due to oedema caused by increased

98/022

- 38 -

permeability of the uterine vasculature and recently Cullinan-Bove and Koos (Endocrinology, 1993,133:829-837) demonstrated a close temporal relationship with increased expression of VEGF mRNA in the uterus. We have found that prior treatment of the rats with a neutralising monoclonal antibody to VEGF significantly reduces the acute increase in uterine weight, confirming that the increase in weight is substantially mediated by VEGF.

Groups of 20 to 22-day old rats were treated with a single subcutaneous dose of oestradiol benzoate (2.5µg/rat) in a solvent, or solvent only. The latter served as unstimulated controls. Test compounds were orally administered at various times prior to the administration of oestradiol benzoate. Five hours after the administration of oestradiol benzoate the rats were humanely sacrificed and their uteri were dissected, blotted and weighed. The increase in uterine weight in groups treated with test compound and oestradiol benzoate and with oestradiol benzoate alone was compared using a Student T test. Inhibition of the effect of oestradiol benzoate was considered significant when $p < 0.05$.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula I as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream or for rectal administration for example as a suppository. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compositions of the present invention are advantageously presented in unit dosage form. The compound will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000mg per square metre body area of the animal, i.e. approximately 0.1-100mg/kg. A unit dose in the range, for example, 1-100mg/kg, preferably 1-50mg/kg is envisaged and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250mg of active ingredient.

98/022

- 39 -

According to a further aspect of the present invention there is provided a compound of the formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

5 We have found that compounds of the present invention inhibit VEGF receptor tyrosine kinase activity and are therefore of interest for their antiangiogenic effects and/or their ability to cause a reduction in vascular permeability.

10 A further feature of the present invention is a compound of formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament, conveniently a compound of formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being.

15 Thus according to a further aspect of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being.

20 According to a further feature of the invention there is provided a method for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore.

25 As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

30 The antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice

98/022

- 40 -

to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

- (i) other antiangiogenic agents that work by different mechanisms from those defined hereinbefore (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function, angiostatin, razoxin, thalidomide);
- (ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, idoxifene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone 5 α -dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and
- (iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan).

As stated above the compounds defined in the present invention are of interest for their antiangiogenic and/or vascular permeability reducing effects. Such compounds of the invention are expected to be useful in a wide range of disease states including cancer,

98/022

- 41 -

diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. In particular such compounds of the invention are expected to slow
5 advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with VEGF, especially those tumours which are significantly dependent on VEGF for their growth and spread, including for example, certain tumours of the colon, breast,
10 prostate, lung, vulva and skin.

In addition to their use in therapeutic medicine, the compounds of formula I and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of in vitro and in vivo test systems for the evaluation of the effects of inhibitors of VEGF receptor tyrosine kinase activity in laboratory animals such as
15 cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

It is to be understood that where the term "ether" is used anywhere in this specification it refers to diethyl ether.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:-

20 (i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid
25 chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

30 (v) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus, an oil-bath apparatus or a Koffler hot plate apparatus.

98/022

- 42 -

(vi) the structures of the end-products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin,
5 quintet;

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(viii) petroleum ether refers to that fraction boiling between 40-60°C

10 (ix) the following abbreviations have been used:-

DMF *N,N*-dimethylformamide

DMSO dimethylsulphoxide

TFA trifluoroacetic acid

15 NMP 1-methyl-2-pyrrolidinone

THF tetrahydrofuran.

Example 1

20 3-Phenyl-4,5-dihydro-1*H*-pyrazol-5-one (160mg, 1mmol), (J. Org. Chem., 1967, 32, 3321-3324), was added in portions over 10 minutes to a suspension of sodium hydride (40mg, 1mmol, prewashed with THF) in DMF (3ml) under nitrogen. After stirring for 20 minutes at ambient temperature 4-chloro-6,7-dimethoxyquinazoline (112mg, 0.5mmol) was added and the mixture was heated for 20 minutes at 60°C. After cooling, the mixture was diluted with
25 saturated aqueous ammonium chloride solution and partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried (MgSO₄) and the volatiles removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5 followed by 90/10). The volatiles were removed by evaporation, the residual solid was dissolved in methylene chloride and 3M ethereal hydrogen chloride (1ml) was added. After removal of the solvent by evaporation, the residue was
30 triturated with ether, collected by filtration and dried under vacuum to give **6,7-dimethoxy-4-(5-phenylpyrazol-3-yloxy)quinazoline** (145mg, 75%).

98/022

- 43 -

¹H NMR Spectrum: (DMSO-d₆; CF₃COOD) 3.98(s, 3H); 3.99(s, 3H); 6.66(s, 1H); 7.33(t, 1H); 7.43(t, 2H); 7.45(s, 1H); 7.62(s, 1H); 7.73(d, 1H); 8.9(s, 1H)

MS - ESI: 349 [MH]⁺

The starting material was prepared as follows:

5 A mixture of 4,5-dimethoxyanthranilic acid (19.7g) and formamide (10ml) was stirred and heated at 190°C for 5 hours. The mixture was allowed to cool to approximately 80°C and water (50ml) was added. The mixture was then allowed to stand at ambient temperature for 3 hours. The precipitate was collected by filtration, washed with water and dried to give 6,7-dimethoxy-3,4-dihydroquinazolin-4-one (3.65g).

10 To a portion (2.06g) of the material so obtained were added thionyl chloride (20ml) and DMF (1 drop) and the mixture stirred and heated at reflux for 2 hours. Excess thionyl chloride was removed by evaporation and the residue was partitioned between ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution. The organic phase was washed with water, dried (MgSO₄) and the solvent removed by evaporation. The residue was purified
15 by column chromatography using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent to give 4-chloro-6,7-dimethoxyquinazoline (0.6g, 27%).

Example 2

20 3-Benzyl-4,5-dihydro-1H-pyrazol-5-one (174mg, 1mmol), (J. Chem. Soc. Perk. Trans 1, 1980, 1618-1621), was added to a suspension of sodium hydride (40mg, 1mmol, prewashed with pentane) in DMF (3ml) under nitrogen. After stirring for 30 minutes at ambient temperature, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (135mg, 0.4mmol) was added and the mixture was heated at 80°C for 1 hour. After cooling, the mixture was diluted with saturated aqueous ammonium chloride solution and partitioned between ethyl
25 acetate and water. The precipitate was collected by filtration, washed with water, followed by ethanol, ether and dried under vacuum to give 4-(5-benzylpyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (150mg, 79%).

¹H NMR Spectrum: (DMSO-d₆; CF₃COOD) 2.35-2.45(m, 2H); 3.15-3.3(m, 2H); 3.45(t, 2H); 3.65(d, 2H); 3.75(t, 2H); 4.10(s, 3H); 4.11(s, 2H); 4.15(d, 2H); 4.45(d, 2H); 6.12(s, 1H); 7.3-
30 7.5(m, 5H); 7.58(s, 1H); 7.75(s, 1H); 9.05(s, 1H)

MS - ESI: 476 [MH]⁺

98/022

- 44 -

The starting material was prepared as follows:

A mixture of 4-hydroxy-3-methoxybenzoic acid (4.5g, 26.8mmol), 3-morpholinopropyl chloride (9.5g, 58.0mmol), (prepared according to J. Am. Chem. Soc. 1945, 67, 736), potassium carbonate (8.0g, 58mmol), potassium iodide (1.0g, 0.22mmol) and
5 DMF (80ml) was stirred and heated at 100°C for 3 hours. The solid was removed by filtration and the volatiles were removed by evaporation. The residue was dissolved in ethanol (50ml), 2M sodium hydroxide (50ml) was added and the mixture heated at 90°C for 2 hours. After partial evaporation, the mixture was acidified with concentrated hydrochloric acid, washed with ether and then subjected to purification on a Diaion (trade mark of Mitsubishi) HP20SS
10 resin column, eluting with water and then with a gradient of methanol (0 to 25%) in hydrochloric acid (pH2). Partial evaporation of the solvents and lyophilisation gave 3-methoxy-4-(3-morpholinopropoxy)benzoic acid (8.65g, 97%).

¹H NMR Spectrum: (DMSO-d₆; TFA) 2.17-2.24(m, 2H); 3.10-3.16(m, 2H); 3.30(t, 2H); 3.52(d, 2H); 3.71(t, 2H); 3.82(s, 3H); 4.01(br d, 2H); 4.14(t, 2H); 7.08(d, 1H); 7.48(d, 1H);
15 7.59(dd, 1H)

MS - ESI: 296 [MH]⁺

Fuming nitric acid (1.5ml, 36.2mmol) was added slowly at 0°C to a solution of 3-methoxy-4-(3-morpholinopropoxy)benzoic acid (7.78g, 23.5mmol) in TFA (25ml). The cooling bath was removed and the reaction mixture stirred at ambient temperature for 1 hour.
20 The TFA was removed by evaporation and ice was added to the residue. The precipitate was collected by filtration, washed with a minimum of water followed by toluene and ether. The solid was dried under vacuum over phosphorus pentoxide to give 5-methoxy-4-(3-morpholinopropoxy)-2-nitrobenzoic acid (7.54g) which was used without further purification.
¹H NMR Spectrum: (DMSO-d₆; TFA) 2.16-2.23(m, 2H); 3.10-3.17(m, 2H); 3.30(t, 2H);
25 3.52(d, 2H); 3.66(t, 2H); 3.93(s, 3H); 4.02(br d, 2H); 4.23(t, 2H); 7.34(s, 1H); 7.61(s, 1H)
MS - EI: 340 [M]⁺

Thionyl chloride (15ml) and DMF (0.05ml) were added to 5-methoxy-4-(3-morpholinopropoxy)-2-nitrobenzoic acid (7.54g). The mixture was heated at 50°C for 1 hour, the excess thionyl chloride was removed by evaporation and by azeotropeing with toluene (x2).
30 The resulting solid was suspended in THF (200ml) and ammonia was bubbled through the mixture for 30 minutes. The precipitate was removed by filtration and washed with THF. After concentration of the filtrate by evaporation, the product crystallised and was collected by

98/022

- 45 -

filtration to give 5-methoxy-4-(3-morpholinopropoxy)-2-nitrobenzamide (5.25g) as light yellow crystals which were used without further purification.

¹H NMR Spectrum: (DMSO-d₆; TFA) 2.17-2.24(m, 2H); 3.11-3.18(m, 2H); 3.31(t, 2H); 3.53(d, 2H); 3.67(t, 2H); 3.93(s, 3H); 4.03(br d, 2H); 4.21(t, 2H); 7.17(s, 1H); 7.62(s, 1H)

5 MS - EI: 339 [M]⁺

Concentrated hydrochloric acid (30ml) was added to a suspension of 5-methoxy-4-(3-morpholinopropoxy)-2-nitrobenzamide (5.67g) in methanol (150ml) and the mixture was heated to 60°C. When the 5-methoxy-4-(3-morpholinopropoxy)-2-nitrobenzamide had dissolved, iron powder (5.6g, 100mmol) was added in portions to the reaction mixture which was then heated for 90 minutes. After cooling, the insolubles were removed by filtration through diatomaceous earth, the volatiles were removed from the filtrate by evaporation and the residue was purified on a Diaion (trade mark of Mitsubishi) HP20SS resin column, eluting with water and then with hydrochloric acid (pH2). Concentration of the fractions by evaporation gave a precipitate which was collected by filtration and dried under vacuum over phosphorus pentoxide to give 2-amino-5-methoxy-4-(3-morpholinopropoxy)benzamide as a hydrochloride salt (4.67g, 75%) as beige crystals.

¹H NMR Spectrum: (DMSO-d₆; TFA) 2.22-2.28(m, 2H); 3.12(br t, 2H); 3.29(t, 2H); 3.51(d, 2H); 3.75(t, 2H); 3.87(s, 3H); 4.00(br d, 2H); 4.12(t, 2H); 7.06(s, 1H); 7.53(s, 1H)

MS - EI: 309 [M]⁺

A mixture of 2-amino-5-methoxy-4-(3-morpholinopropoxy)benzamide (4.57g, 12.25mmol) and Gold's reagent (2.6g, 15.89mmol) in dioxane (35ml) was heated at reflux for 5 hours. Acetic acid (0.55ml) and sodium acetate (1.0g) were added to the reaction mixture which was heated for a further 3 hours. The mixture was cooled to ambient temperature and the volatiles removed by evaporation. The residue was adjusted to pH7 with 2M sodium hydroxide and then purified on a Diaion (trade mark of Mitsubishi) HP20SS resin column, eluting with methanol (gradient of 0 to 60%) in water. Concentration of the fractions by evaporation gave a precipitate which was collected by filtration and dried under vacuum over phosphorus pentoxide to give 4-hydroxy-6-methoxy-7-(3-morpholinopropoxy)quinazoline (3.04g, 78%) as a white solid.

¹H NMR Spectrum: (CDCl₃) 2.10(q, 2H); 2.48(m, 4H); 2.56(t, 2H); 3.72(t, 4H); 4.00(s, 3H); 4.24(t, 2H); 7.18(s, 1H); 7.60(s, 1H); 8.00(s, 1H); 10.86(br s, 1H)

MS - EI: 319 [M]⁺

98/022

- 46 -

A mixture of 4-hydroxy-6-methoxy-7-(3-morpholinopropoxy)quinazoline (638mg, 2mmol) and thionyl chloride (8ml) was heated at reflux for 30 minutes. Excess thionyl chloride was removed by evaporation and by azeotrope with toluene (x2). The residue was suspended in methylene chloride and 10% aqueous solution of sodium hydrogen carbonate was added to the mixture. The organic layer was separated, dried (MgSO₄) and the solvent removed by evaporation. The residue was triturated with ether, the solid was collected by filtration, washed with ether and dried under vacuum to give 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (590mg, 87%).

¹H NMR Spectrum: (CDCl₃) 2.10-2.16(m, 2H); 2.48(br s, 4H); 2.57(t, 2H); 3.73(t, 4H); 4.05(s, 3H); 4.29(t, 2H); 7.36(s, 1H); 7.39(s, 1H); 8.86(s, 1H)

MS - ESI: 337 [MH]⁺

Example 3

Using an analogous procedure to that described for Example 2, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (169mg, 0.5mmol), (prepared as described for the starting material in Example 2), was reacted with 3-phenyl-4,5-dihydro-1H-pyrazol-5-one (200mg, 1.25mmol), (J. Org. Chem., 1967, 32, 3321-3324), in the presence of sodium hydride (50mg, 1.25mmol, prewashed with pentane) in DMF (3ml) to give 6-methoxy-7-(3-morpholinopropoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline as the free base. The free base was dissolved in a mixture of methylene chloride/methanol (1/1) and 3M hydrochloric acid in methanol was added. The volatiles were removed by evaporation to give 6-methoxy-7-(3-morpholinopropoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline hydrochloride (115mg, 43%).

¹H NMR Spectrum: (DMSO-d₆; CF₃COOD) 2.3-2.4(m, 2H); 3.15(t, 2H); 3.3-3.4(m, 2H); 3.55(d, 2H); 3.75(t, 2H); 4.01(d, 2H); 4.05(s, 3H); 4.38(t, 2H); 6.7(s, 1H); 7.4(t, 1H); 7.5(t, 2H); 7.55(s, 1H); 7.7(s, 1H); 7.8(d, 2H); 8.91(s, 1H)

MS - EI: 461 [M]⁺

Elemental analysis:

C₂₅H₂₇N₅O₄ 0.7H₂O 2HCl

Found

C 53.0 H 5.8 N 12.3

Requires

C 53.1 H 5.7 N 12.9%

30

98/022

- 47 -

Example 4

Using an analogous procedure to that described for Example 1, 4-chloro-6-methoxy-7-(2-methoxyethoxy)quinazoline (134mg, 0.5mmol) was reacted with 3-phenyl-4,5-dihydro-1H-pyrazol-5-one (160mg, 1mmol), (J. Org. Chem., 1967, 32, 3321-3324), in the presence of sodium hydride (40mg, 1mmol, prewashed with THF) in DMF (3ml) to give 6-methoxy-7-(2-methoxyethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline as the free base. The free base was dissolved in a mixture of methylene chloride/methanol (1/1) and 3M hydrochloric acid in methanol was added. The volatiles were removed by evaporation to give 6-methoxy-7-(2-methoxyethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline hydrochloride (155mg, 72%).

¹H NMR Spectrum: (DMSO-d₆; CF₃COOD) 3.38(s, 3H); 3.85(t, 2H); 4.09(s, 3H); 4.43(t, 2H); 6.74(s, 1H); 7.42(t, 1H); 7.51(t, 2H); 7.58(s, 1H); 7.76(s, 1H); 7.82(d, 2H); 9.15(s, 1H)

MS - EI: 392 [M.]⁺

Elemental analysis:	Found	C 56.0	H 5.3	N 12.3
C ₂₁ H ₂₀ N ₄ O ₄ 1.6H ₂ O 0.75HCl	Requires	C 56.2	H 5.4	N 12.5%

The starting material was prepared as follows:

A mixture of ethyl 4-hydroxy-3-methoxybenzoate (9.8g, 50mmol), 2-bromoethyl methyl ether (8.46ml, 90mmol) and potassium carbonate (12.42g, 90mmol) in acetone (60ml) was heated at reflux for 30 hours. The mixture was allowed to cool and the solids removed by filtration. The volatiles were removed from the filtrate by evaporation and the residue triturated with hexane to give ethyl 3-methoxy-4-(2-methoxyethoxy)benzoate (11.3g, 89%) as a white solid.

m.p. 57-60°C

¹H NMR Spectrum: (DMSO-d₆) 1.31(t, 3H); 3.29(s, 3H); 3.32(s, 3H); 3.68(m, 2H); 4.16(m, 2H); 4.28(q, 2H); 7.06(d, 1H); 7.45(d, 1H); 7.56(dd, 1H)

MS - FAB: 255 [MH]⁺

Ethyl 3-methoxy-4-(2-methoxyethoxy)benzoate (9.5g, 37mmol) was added in portions to stirred concentrated nitric acid (75ml) at 0°C. The mixture was allowed to warm to ambient temperature and stirred for a further 90 minutes. The mixture was diluted with water and extracted with methylene chloride, dried (MgSO₄) and the solvent removed by evaporation. The residue was triturated with hexane to give ethyl 5-methoxy-4-(2-methoxyethoxy)-2-nitrobenzoate (10.6g, 95%) as an orange solid.

98/022

- 48 -

m.p. 68-69°C

¹H NMR Spectrum: (DMSO-d₆) 1.27(t, 3H); 3.30(s, 3H); 3.69(m, 2H); 3.92(s, 3H); 4.25(m, 2H); 4.29(q, 2H); 7.30(s, 1H); 7.65(s, 1H)

MS - CI: 300 [MH]⁺

- 5 A mixture of ethyl 5-methoxy-4-(2-methoxyethoxy)-2-nitrobenzoate (10.24g, 34mmol), cyclohexene (30ml) and 10% palladium-on-charcoal catalyst (2.0g) in methanol (150ml) was heated at reflux for 5 hours. The reaction mixture was allowed to cool and diluted with methylene chloride. The catalyst was removed by filtration and the volatiles removed from the filtrate by evaporation. The residue was recrystallised from ethyl acetate/hexane to give ethyl 2-amino-5-methoxy-4-(2-methoxyethoxy) benzoate (8.0g) as a buff solid. Formamide (80ml) was added to this product and the mixture heated at 170°C for 18 hours. About half the solvent was removed by evaporation under high vacuum and the residue was left to stand overnight. The solid product was collected by filtration, washed with ether and dried to give 6-methoxy-7-(2-methoxyethoxy)-3,4-dihydroquinazolin-4-one (5.3g, 15 62% over two steps) as a grey solid.

¹H NMR Spectrum: (DMSO-d₆) 3.35(s, 3H); 3.74(m, 2H); 3.89(s, 3H); 4.26(m, 2H); 7.15(s, 1H); 7.47(s, 1H); 7.98(s, 1H); 12.03(br s, 1 H)

MS - CI: 251 [MH]⁺

- DMF (0.5ml) was added to a mixture of 6-methoxy-7-(2-methoxyethoxy)-3,4-dihydroquinazolin-4-one (5.1g, 20mmol) in thionyl chloride (50ml). The mixture was stirred and heated at reflux for 3 hours, allowed to cool and the excess thionyl chloride removed by evaporation. The residue was suspended in methylene chloride and washed with aqueous sodium hydrogen carbonate solution. The aqueous phase was extracted with methylene chloride and the combined extracts dried (MgSO₄). The crude product was recrystallised from 25 methylene chloride/hexane to give 4-chloro-6-methoxy-7-(2-methoxyethoxy)quinazoline (2.8g, 51%) as a fine white solid.

¹H NMR Spectrum: (DMSO-d₆) 3.37(s, 3H); 3.77(m, 2H); 4.01(s, 3H); 4.37(m, 2H); 7.40(s, 1H); 7.49(s, 1H); 8.88(s, 1H)

MS - CI: 269 [MH]⁺

30

98/022

- 49 -

Example 5

3-(4-Fluorophenyl)-4,5-dihydro-1*H*-pyrazol-5-one (222mg, 1.25mmol) was added in portions over 10 minutes to a suspension of sodium hydride (50mg, 1.25mmol, prewashed with hexane) in DMF (3ml) under nitrogen. After stirring for 20 minutes at ambient temperature, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (169mg, 0.5mmol), (prepared as described for the starting material in Example 2), was added and the mixture was heated at 60°C for 1 hour. After cooling, the mixture was diluted with aqueous ammonium chloride solution and ether was added. The precipitate was collected by filtration, washed with water, and dried under vacuum. The solid was dissolved in methylene chloride/methanol (1/1) and 4M ethereal hydrogen chloride (0.5ml) was added. After removal of the solvent by evaporation, the solid was triturated with ether, collected by filtration and dried under vacuum to give 4-(5-(4-fluorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline hydrochloride (115mg, 48%).

¹H NMR Spectrum: (DMSO-d₆; CF₃COOD) 2.3-2.4(m, 2H); 3.1-3.2(m, 2H); 3.35(t, 2H); 3.55(d, 2H); 3.75(t, 2H); 4.02(d, 2H); 4.04(s, 3H); 4.35(t, 2H); 6.71(s, 1H); 7.35(t, 2H); 7.53(s, 1H); 7.67(s, 1H); 7.83(dd, 2H); 8.86(s, 1H)

MS - ESI: 480 [MH]⁺

Elemental analysis:	Found	C 52.7	H 5.4	N 12.5
C ₂₅ H ₂₆ N ₅ O ₄ F 1.2H ₂ O 1.9HCl	Requires	C 52.6	H 5.3	N 12.3%

The starting material was prepared as follows:

To a solution of methyl 4-fluorobenzoyl acetate (588mg, 3mmol), (Clark, J.Chem. Soc. 1971, 1945) in ethanol (6ml) was added hydrazine hydrate (150mg, 3mmol). After stirring for 30 minutes at ambient temperature, the mixture was stirred at 80°C for 30 minutes. After cooling, ether was added. The precipitate was collected by filtration, washed with ether and dried under vacuum to give 3-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-5-one (504mg, 94%).

¹H NMR Spectrum: (DMSO-d₆; CF₃COOD) 6.2(d, 0.25H, enolic proton partly exchanged); 7.35(t, 2H); 7.8-7.9(m, 2H)

MS - EI: 178 [M]⁺

Elemental analysis:	Found	C 60.8	H 4.0	N 15.9
---------------------	-------	--------	-------	--------

98/022

- 50 -

 $C_9H_7N_2OF$

Requires

C 60.8 H 4.0 N 15.7%

Example 6

3-Phenyl-4,5-dihydro-1*H*-pyrazol-5-one (270mg, 1.68 mmol), (J. Org. Chem., 1967, 32, 3321-3324), was added in portions over 10 minutes to a suspension of sodium hydride (70mg, 1.68mmol, prewashed with pentane) in DMF (3ml) under nitrogen. After stirring for 1 hour at ambient temperature 4-chloro-7-(2-methoxyethoxy)quinazoline (160mg, 0.67mmol) was added and the mixture was heated for 1 hour at 60°C. After cooling, the mixture was diluted with saturated aqueous ammonium chloride solution and partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried ($MgSO_4$) and the volatiles removed by evaporation. The residue was purified by column chromatography eluting with methanol/methylene chloride (5/95). The volatiles were removed by evaporation, the residual solid was dissolved in methylene chloride and 3M ethereal hydrogen chloride (0.5ml) was added. After removal of the solvent by evaporation, the residue was triturated with ether, collected by filtration and dried under vacuum to give 7-(2-methoxyethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline hydrochloride (120mg, 46%).

1H NMR Spectrum: ($DMSO-d_6$; CF_3COOD) 3.36(s, 3H); 3.8(t, 2H); 4.4(t, 2H); 6.7(s, 1H); 7.4(t, 1H); 7.4-7.55(m, 4H); 7.8(d, 2H); 8.35(d, 1H); 8.94(s, 1H)

MS - ESI: 363 $[MH]^+$

20	Elemental analysis:	Found	C 62.5	H 4.9	N 14.3
	$C_{20}H_{18}N_4O_3 \cdot 0.6HCl$	Requires	C 62.2	H 4.9	N 14.5%

The starting material was prepared as follows:

A solution of 2-amino-4-fluorobenzoic acid (3g, 19.3mmol) in formamide (30ml) was heated at 150°C for 6 hours. The reaction mixture was poured onto ice/water 1/1 (250ml). The precipitated solid was collected by filtration, washed with water and dried to give 7-fluoro-3,4-dihydroquinazolin-4-one (2.6g, 82%).

Sodium (400mg, 17mmol) was added carefully to 2-methoxyethanol (10ml) and the mixture heated at reflux for 30 minutes. 7-Fluoro-3,4-dihydroquinazolin-4-one (750mg, 4.57mmol) was added to the resulting solution and the mixture heated at reflux for 15 hours. The mixture was cooled and poured into water (250ml). The mixture was acidified to pH4 with concentrated hydrochloric acid. The resulting solid product was collected by filtration,

98/022

- 51 -

washed with water and then with ether, and dried under vacuum to give 7-(2-methoxyethoxy)-3,4-dihydroquinazolin-4-one (580mg, 58%).

A solution of 7-(2-methoxyethoxy)-3,4-dihydroquinazolin-4-one (500mg, 2.2mmol) in thionyl chloride (15ml) and DMF (0.1ml) was heated at reflux for 3 hours. The volatiles were removed by evaporation to give 4-chloro-7-(2-methoxyethoxy)quinazoline hydrochloride as a cream solid (520mg, 83%).

A suspension of 4-chloro-7-(2-methoxyethoxy)quinazoline hydrochloride (500mg, 1.8mmol) in a mixture of water (20ml) and ethyl acetate (20ml) was diluted with a saturated solution of sodium hydrogen carbonate. After stirring at ambient temperature for 15 minutes the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried (MgSO₄) and evaporated to give 4-chloro-7-(2-methoxyethoxy)quinazoline (345mg, 80%).

Example 7

Using an analogous procedure to that described for Example 6, 4-chloro-6-methoxy-7-(2-(imidazol-1-yl)ethoxy)quinazoline (0.2g, 0.66mmol) was reacted with 3-phenyl-4,5-dihydro-1H-pyrazol-5-one (260mg, 1.6mmol), (J. Org. Chem., 1967, 32, 3321-3324), in DMF (3ml) containing sodium hydride (65mg, 1.6mmol) to give, after purification, 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-4-(5-phenylpyrazol-3-yloxy)quinazoline hydrochloride (100mg, 28%).

¹H NMR Spectrum: (DMSO-d₆; CF₃COOD) 4.05(s, 3H); 4.70(t, 2H); 4.79(t, 2H); 6.7(s, 1H); 7.4(t, 1H); 7.5(t, 2H); 7.57(s, 1H); 7.7(s, 1H); 7.73(s, 1H); 7.8(d, 1H); 7.85(s, 1H); 8.91(s, 1H); 9.22(s, 1H)

MS - ESI: 429 [MH]⁺

Elemental analysis: Found C 50.6 H 4.5 N 15.3

C₂₃H₂₀N₆O₃ 1.5H₂O 2.5HCl Requires C 50.5 H 4.7 N 15.4%

The starting material was prepared as follows:

A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (10g, 0.04mol), (prepared according to J. Med. Chem. 1977, vol 20, 146-149), and Gold's reagent (7.4g, 0.05mol) in dioxane (100ml) was stirred and heated at reflux for 24 hours. Sodium acetate (3.02g, 0.037mol) and acetic acid (1.65ml, 0.029mol) were added to the reaction mixture and it was heated for a further 3 hours. The volatiles were removed by evaporation, water was added to the residue, the solid was collected by filtration, washed with water and dried. Recrystallisation

98/022

- 52 -

from acetic acid gave 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7g, 84%).

Sodium hydride (1.44g of a 60% suspension in mineral oil, 36mmol) was added in portions over 20 minutes to a solution of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.46g, 30mmol), in DMF (70ml) and the mixture was stirred for 1.5 hours. Chloromethyl
5 pivalate (5.65g, 37.5mmol) was added dropwise and the mixture stirred for 2 hours at ambient temperature. The mixture was diluted with ethyl acetate (100ml) and poured onto ice/water (400ml) and 2M hydrochloric acid (4ml). The organic layer was separated and the aqueous layer extracted with ethyl acetate, the combined extracts were washed with brine, dried (MgSO₄) and the solvent removed by evaporation. The residue was triturated with a mixture of
10 ether and petroleum ether, the solid was collected by filtration and dried under vacuum to give 7-benzyloxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (10g, 84%).

¹H NMR Spectrum: (DMSO-d₆) 1.11(s, 9H); 3.89(s, 3H); 5.3(s, 2H); 5.9(s, 2H); 7.27(s, 1H); 7.35(m, 1H); 7.47(t, 2H); 7.49(d, 2H); 7.51(s, 1H); 8.34(s, 1H)

A mixture of 7-benzyloxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-
15 4-one (7g, 17.7mmol) and 10% palladium-on-charcoal catalyst (700mg) in ethyl acetate (250ml), DMF (50ml), methanol (50ml) and acetic acid (0.7ml) was stirred under hydrogen at atmospheric pressure for 40 minutes. The catalyst was removed by filtration and the solvent removed from the filtrate by evaporation. The residue was triturated with ether, collected by filtration and dried under vacuum to give 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-
20 dihydroquinazolin-4-one (4.36g, 80%).

¹H NMR Spectrum: (DMSO-d₆) 1.1(s, 9H); 3.89(s, 3H); 5.89(s, 2H); 7.0(s, 1H); 7.48(s, 1H); 8.5(s, 1H)

Diethyl azodicarboxylate (435mg, 2.5mmol) was added dropwise to a suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (612mg, 2mmol),
25 2-(imidazol-1-yl)ethanol (280mg, 2.5mmol), (J. Med. Chem. 1993, 25, 4052-4060), and triphenylphosphine (655mg, 2.5mmol) in methylene chloride (10ml) at 5°C. The mixture was stirred for 10 minutes at 5°C and then 1 hour at ambient temperature. The mixture was poured directly on to a silica column and eluted with methylene chloride/methanol (95/5) to give 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-
30 4-one (640mg, 80%).

98/022

- 53 -

¹H NMR Spectrum: (CDCl₃) 1.19(s, 9H); 3.98(s, 3H); 4.34(m, 2H); 4.45(m, 2H); 5.94(s, 2H); 7.02(s, 1H); 7.07(s, 1H); 7.11(s, 1H); 7.64(s, 1H); 7.67(s, 1H); 8.17(s, 1H)

MS - ESI: 423 [MNa]⁺

Elemental analysis:	Found	C 58.3	H 6.4	N 13.9
---------------------	-------	--------	-------	--------

5	C ₂₀ H ₂₄ N ₄ O ₅ 0.7H ₂ O	Requires	C 58.2	H 6.2	N 13.6%
---	---	----------	--------	-------	---------

A solution of 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (640mg, 1.6mmol) in saturated methanolic ammonia (10ml) was stirred for 15 hours at ambient temperature. The volatiles were removed by evaporation, the solid was triturated with ether, collected by filtration and dried under vacuum to give 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (412mg, 90%).

¹H NMR Spectrum: (DMSO-d₆) 3.89(s, 3H); 4.4-4.5(m, 4H); 6.9(s, 1H); 7.16(s, 1H); 7.28(s, 1H); 7.47(s, 1H); 7.7(s, 1H); 7.99(s, 1H)

MS - ESI: 287 [MH]⁺

Elemental Analysis:	Found	C 57.8	H 5.2	N 19.3
---------------------	-------	--------	-------	--------

15	C ₁₄ H ₁₄ N ₄ O ₃ 0.3H ₂ O	Requires	C 57.7	H 5.1	N 19.2%
----	---	----------	--------	-------	---------

A mixture of 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (412mg, 1.44mmol), thionyl chloride (5 ml) and DMF (0.2ml) was heated at reflux for 1 hour. The mixture was diluted with toluene and the volatiles were removed by evaporation. The residue was suspended in methylene chloride, cooled to 0°C and aqueous sodium hydrogen carbonate solution was added. The resulting precipitate was collected by filtration and dried under vacuum to give 4-chloro-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline (258mg, 59%).

¹H NMR Spectrum: (DMSO-d₆) 4.01(s, 3H); 4.47(m, 2H); 4.53(m, 2H); 6.89(s, 1H); 7.27(s, 1H); 7.41(s, 1H); 7.49(s, 1H); 7.70(s, 1H); 8.88(s, 1H)

25	MS - ESI: 327 [MNa] ⁺
----	----------------------------------

Example 8

Using an analogous procedure to that described for Example 6, 4-chloro-6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)quinazoline (156mg, 0.5mmol) was reacted with 3-phenyl-4,5-

98/022

- 54 -

dihydro-1*H*-pyrazol-5-one (200mg, 1.25mmol), (J. Org. Chem., 1967, 32, 3321-3324), in DMF (3ml) containing sodium hydride (50mg, 1.25mmol) to give, after purification, 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline hydrochloride (180mg, 75%).

- 5 ¹H NMR Spectrum: (DMSO-d₆; CF₃COOD) 3.27(s, 3H); 3.52(t, 2H); 3.68(t, 2H); 3.9(t, 2H); 4.04(s, 3H); 4.38(t, 2H); 6.72(s, 1H); 7.4(t, 1H); 7.48(t, 2H); 7.51(s, 1H); 7.67(s, 1H); 7.8(d, 2H); 8.9(s, 1H)

MS - ESI: 437 [MH]⁺

Elemental analysis: Found C 57.5 H 5.8 N 11.7

- 10 C₂₃H₂₄N₄O₅ 0.5H₂O 0.85HCl Requires C 58.0 H 5.5 N 11.8%

The starting material was prepared as follows:

- Diethyl azodicarboxylate (864μl, 5.5mmol) was added dropwise to a mixture of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.2g, 3.9mmol) (prepared as described for the starting material in Example 7), triphenylphosphine (1.44g, 5.5mmol) and 2-(2-methoxyethoxy)ethanol (653μl, 5.5mmol) in methylene chloride (70ml) cooled at 0°C. The mixture was stirred for 1.5 hours at ambient temperature and the solvent was removed by evaporation. The residue was purified by column chromatography eluting with a mixture of ethyl acetate/methylene chloride (50/50 followed by 80/20). The purified solid was suspended in ether, collected by filtration and dried under vacuum to give 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.70g, 100%).
- 15
- 20

¹H NMR Spectrum: (DMSO-d₆) 1.13(s, 9H); 3.26(s, 3H); 3.5(m, 2H); 3.65(m, 2H); 3.85(m, 2H); 3.91(s, 3H); 4.3(m, 2H); 5.9(s, 2H); 7.2(s, 1H); 7.5(s, 1H); 8.4(s, 1H)

- 25 Saturated methanolic ammonia (20ml) was added to a solution of 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (2.26g, 5.5mmol) in a mixture of ethanol (40ml) and methylene chloride (15ml). The mixture was stirred for 24 hours at ambient temperature, and further methanolic ammonia (20ml) was added. The mixture was stirred for a further 24 hours at ambient temperature and the volatiles were removed by evaporation. The residue was triturated with ether, collected by filtration, dried under vacuum to give 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-3,4-dihydroquinazolin-4-one (975mg, 78%).
- 30

98/022

- 55 -

¹H NMR Spectrum: (DMSO-d₆) 3.25(s, 3H); 3.45(t, 2H); 3.6(t, 2H); 3.8(t, 2H); 3.9(s, 3H); 4.2(t, 2H); 7.15(s, 1H); 7.45(s, 1H); 8.0(s, 1H)

MS - EI: 294 [M]⁺

A solution of 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-3,4-dihydroquinazolin-4-one (930mg, 3.16mmol) in thionyl chloride (15ml) and DMF (150μl) was heated at 60°C for 1.5 hours. The mixture was allowed to cool and the volatiles were removed by evaporation and by azeotroping with toluene. The residue was dissolved in methylene chloride and 5% aqueous sodium hydrogen carbonate solution was added until the aqueous layer was at pH8. The organic layer was separated, washed with brine, dried (MgSO₄) and the solvent removed by evaporation. The residue was purified by flash chromatography eluting with ethyl acetate to give 4-chloro-6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)quinazoline (863mg, 87%).

¹H NMR Spectrum: (DMSO-d₆) 3.24(s, 3H); 3.47(m, 2H); 3.62(m, 2H); 3.84(t, 2H); 4.01(s, 3H); 4.25(t, 2H); 7.41(s, 1H); 7.49(s, 1H); 8.88(s, 1H)

15 Example 9

Sodium hydride (40mg, 1mmol, prewashed with THF) was added to a suspension of 3-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-5-one (220mg, 1mmol) in DMF (3ml) under nitrogen. After stirring for 20 minutes at ambient temperature, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (134mg, 0.4mmol), (prepared as described for the starting material in Example 2), was added and the mixture was heated for 30 minutes at 60°C. After cooling, the mixture was diluted with saturated aqueous ammonium chloride solution and partitioned between methylene chloride and water. The organic layer was washed with water, brine, dried (MgSO₄) and the volatiles were removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/ethyl acetate/methanol (1/1/0 followed by 5/4/1). The volatiles were removed by evaporation and the residual solid was collected by filtration, washed with ether and dried under vacuum to give 4-(5-(3,4-dimethoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (120mg, 57%).

¹H NMR Spectrum: (DMSO-d₆) 1.95-2.05(m, 2H); 2.4-2.6(m, 6H); 3.6(t, 4H); 3.81(s, 3H); 3.85(s, 3H); 4.02(s, 3H); 4.3(t, 2H); 6.65(s, 1H); 7.05(d, 1H); 7.35(d, 1H); 7.42(d, 2H); 7.55(s, 1H); 8.65(s, 1H)

98/022

- 56 -

MS - ESI: 522 [MH]⁺

Elemental analysis:	Found	C 61.5	H 6.1	N 13.0
C ₂₇ H ₃₁ N ₅ O ₆ 0.2H ₂ O 0.12Et ₂ O	Requires	C 61.8	H 6.1	N 13.1%

5 The starting material was prepared as follows:

A solution of ethyl-3,4-dimethoxybenzoylacetate (1g, 4mmol), (Heterocycles 1979, 13, 239), in ethanol (5ml) containing hydrazine hydrate (192μl, 4mmol) was stirred for 30 minutes at ambient temperature followed by 40 minutes being heated at reflux. After cooling at ambient temperature, the mixture was concentrated to half the volume and ether (10ml) was added. After trituration, the solid was collected by filtration, washed with ether and dried under vacuum to give 3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-one (521mg, 60%).
¹H NMR Spectrum: (DMSO-d₆) 3.76(s, 3H); 3.80(s, 3H); 5.81(s, 1H); 6.96(d, 1H); 7.18(dd, 1H); 7.25(d, 1H)

MS - ESI: 221 [MH]⁺

15

Example 10

Using an analogous procedure to that described in Example 9, 4-chloro-6-methoxy-7-(2-methoxyethoxy)quinazoline (134mg, 0.5mmol), (prepared as described for the starting material in Example 4), was reacted with 3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-one (190mg, 1mmol) in the presence of sodium hydride (40mg, 1mmol, prewashed with THF) in DMF (3ml) to give 6-methoxy-7-(2-methoxyethoxy)-4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)quinazoline (125mg, 59%).

¹H NMR Spectrum: (DMSO-d₆) 3.36(s, 3H); 3.8(t, 2H); 3.82(s, 3H); 4.01(s, 3H); 4.35(t, 2H); 6.6(s, 1H); 7.05(d, 2H); 7.45(s, 1H); 7.55(s, 1H); 7.75(d, 2H); 8.65(s, 1H)

25 MS - ESI: 423 [MH]⁺

Elemental analysis:	Found	C 61.0	H 5.2	N 13.0
C ₂₂ H ₂₂ N ₄ O ₅ 0.5H ₂ O	Requires	C 61.2	H 5.4	N 13.0%

30 The starting material was prepared using an analogous procedure to that described for the synthesis of 3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-one in Example 9. Ethyl-4-methoxybenzoylacetate (1g, 4.5mmol) was reacted with hydrazine hydrate (218μl, 4.5mmol) to give 3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-one (570mg, 67%).

98/022

- 57 -

¹H NMR Spectrum: (DMSO-d₆) 3.77(s, 3H); 5.77(s, 1H); 6.96(d, 2H); 7.60(d, 2H)

MS - ESI: 191 [MH]⁺

Example 11

5 Using an analogous procedure to that described in Example 9, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (134mg, 0.4mmol), (prepared as described for the starting material in Example 2), was reacted with 3-(3-pyridyl)-4,5-dihydro-1H-pyrazol-5-one (161mg, 1mmol) in the presence of sodium hydride (40mg, 1 mmol, prewashed with THF) in DMF (3ml) to give 6-methoxy-7-(3-morpholinopropoxy)-4-(5-(3-pyridyl)pyrazol-3-yloxy)quinazoline (110mg, 59%).

¹H NMR Spectrum: (DMSO-d₆) 1.95-2.05(m, 2H); 2.4(br s, 4H); 2.5(t, 2H); 3.6(t, 4H); 4.02(s, 3H); 4.28(t, 2H); 6.85(s, 1H); 7.45(s, 1H); 7.55(m, 1H); 7.6(s, 1H); 8.3(d, 1H); 8.6(d, 1H); 8.65(s, 1H); 9.05(s, 1H)

MS - ESI: 463 [MH]⁺

15	Elemental analysis:	Found	C 62.2	H 5.7	N 18.0
	C ₂₄ H ₂₆ N ₆ O ₄	Requires	C 62.3	H 5.7	N 18.2%

20 The starting material was prepared using an analogous procedure to that described in Example 9. Ethyl-2-(3-pyridylcarbonyl)acetate (1g, 5.18mmol) was treated with hydrazine hydrate (251μl, 5.2mmol) to give 3-(3-pyridyl)-4,5-dihydro-1H-pyrazol-5-one (413mg, 50%).

¹H NMR Spectrum: (DMSO-d₆) 6.0(br s, 1H); 7.4(m, 1H); 8.05(m, 1H); 8.5(d, 1H); 8.92(s, 1H); 9.7-10(br s, 1H)

MS (ESI) : 162 [MH]⁺

25 Example 12

Using an analogous procedure to that described in Example 9, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (140mg, 0.415mmol), (prepared as described for the starting material in Example 2), was reacted with 3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-one (202mg, 1.04mmol) in the presence of sodium hydride (41.5mg, 1.04mmol, prewashed with THF) in DMF (2.5ml) to give 4-(5-(4-chlorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinaz line (150mg, 73%).

30

98/022

- 58 -

¹H NMR Spectrum: (DMSO-d₆) 1.95-2.05(m, 2H); 2.4(br s, 4H); 2.5(t, 2H); 3.6(t, 4H); 4.0(s, 3H); 4.25(t, 2H); 6.76(s, 1H); 7.42(s, 1H); 7.55(s, 1H); 7.6(d, 2H); 7.85(d, 2H); 8.65(s, 1H)
MS (ESI): 496 [MH]⁺

- 5 The starting material was prepared using an analogous procedure to that described in Example 9. Ethyl-4-chlorobenzoyl acetate (734mg, 3.24mmol) was treated with hydrazine hydrate (157μl, 3.24mmol) to give 3-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-5-one (244mg, 39%).
- ¹H NMR Spectrum: (DMSO-d₆) 5.9(br s, 1H); 7.45(d, 2H); 7.7(d, 2H); 9.7-10(br s, 1H)
- 10 MS (ESI): 195 [MH]⁺

Example 13

- Using an analogous procedure to that described in Example 9, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (200mg, 0.59mmol), (prepared as described for the
- 15 starting material in Example 2), was reacted with 3-(4-pyridyl)-4,5-dihydro-1*H*-pyrazol-5-one (240mg, 1.5mmol) in the presence of sodium hydride (59mg, 1.5mmol, prewashed with THF) in DMF (3ml) to give 6-methoxy-7-(3-morpholinopropoxy)-4-(5-(4-pyridyl)pyrazol-3-yloxy)quinazoline (130mg, 48%).
- ¹H NMR Spectrum: (DMSO-d₆) 1.95-2.05(m, 2H); 2.4(br s, 4H); 2.45(t, 2H); 3.6(t, 4H); 4.0(s, 3H); 4.25(t, 2H); 6.95(s, 1H); 7.4(s, 1H); 7.55(s, 1H); 7.8(d, 2H); 8.62(s, 1H); 8.68(d, 2H)
- 20 MS (ESI): 463 [MH]⁺

Elemental analysis:	Found	C 61.2	H 5.9	N 17.8
C ₂₄ H ₂₆ N ₆ O ₄ · 0.5H ₂ O	Requires	C 61.1	H 5.8	N 17.8 %

- 25 The starting material was prepared using an analogous procedure to that described in Example 9. Ethyl isonicotinoyl acetate (1g, 5.2mmol) was treated with hydrazine hydrate (251μl, 5.2mmol) in ethanol (5ml) to give 3-(4-pyridyl)-4,5-dihydro-1*H*-pyrazol-5-one (714mg, 86%).
- ¹H NMR Spectrum: (DMSO-d₆) 5.9-6.2(br s, 1H); 7.63(d, 2H); 8.6(br s, 2H)
- 30 MS (ESI): 162 [MH]⁺

98/022

- 59 -

Example 14

3-Phenyl-4,5-dihydro-1*H*-pyrazol-5-one (182mg, 1.14mmol) was added in portions to a suspension of sodium hydride (46mg, 1.14mmol, prewashed with pentane) in DMF (3ml). After stirring for 30 minutes at ambient temperature, 4-chloro-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (200mg, 0.57mmol) was added. The mixture was stirred for 30 minutes at 60°C. After cooling, the mixture was diluted with saturated aqueous ammonium chloride solution and partitioned between ethyl acetate and water. The organic layer was passed through an ISOLUTE (trade mark of IST) SPE column. The column was thoroughly washed with methanol. The product was recovered from the column by washing with a mixture of 0.1M solution of ammonia in methylene chloride/methanol (1/1). The volatiles were removed by evaporation and the solid was collected by filtration, washed with ether and dried under vacuum to give 6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline (206mg, 76%).

¹H NMR Spectrum: (DMSO-d₆; CF₃COOD) 2.3-2.4(m, 2H); 2.98(s, 3H); 3.3-3.6(m, 5H); 3.6-4.0(m, 5H); 4.04(s, 3H); 4.38(t, 2H); 6.75(s, 1H); 7.42(s, 1H); 7.5(t, 2H); 7.55(s, 1H); 7.7(s, 1H); 7.85(d, 2H); 8.9(s, 1H)

MS (ESI): 475 [MH]⁺

The starting material was prepared as follows:

1-Bromo-3-chloropropane (0.97ml, 9.8mmol) was added to a solution of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (2.5g, 8.17mmol), (prepared as described for the starting material in Example 7), in DMF (40ml) containing potassium carbonate (2.8g, 20mmol). The mixture was stirred overnight at ambient temperature and partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried (MgSO₄) and evaporated to give 7-(3-chloropropoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (3.10g, 100%).

¹H NMR Spectrum: (DMSO-d₆) 1.12(s, 9H); 2.15(t, 2H); 3.8(t, 2H); 3.9(s, 3H); 4.25(t, 2H); 5.9(s, 2H); 7.2(s, 1H); 7.5(s, 1H); 8.36(s, 1H)

MS (ESI): 383 [MH]⁺

A solution of 7-(3-chloropropoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (3g, 7.84mmol) in 1-methylpiperazine (30ml) was heated at 100°C for 1 hour. After cooling, the mixture was partitioned between saturated ammonium chloride

98/022

- 60 -

and methylene chloride. The organic layer was washed with water, brine, dried (MgSO₄) and the volatiles were removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5 followed by 90/10). The volatiles were removed by evaporation to give 6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (3.24g, 92%).

A solution of 6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (3.1g, 7mmol) in 5M ammonia in methanol (60ml) was stirred at ambient temperature overnight. The volatiles were removed by evaporation and the residue was triturated with ether, collected by filtration, washed with ether and dried under vacuum to give 6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-3,4-dihydroquinazolin-4-one (2.1g, 91%).

¹H NMR Spectrum: (DMSO-d₆) 1.9-2.0(m, 2H); 2.2(s, 3H); 2.2-2.5(m, 10 H); 3.85(s, 3H); 4.15(t, 2H); 7.1(s, 1H); 7.45(s, 1H); 7.95(s, 1H)

MS (ESI): 331 [MH]⁺

A solution of 6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-3,4-dihydroquinazolin-4-one (2.05g, 6.2mmol) in thionyl chloride (30ml) containing DMF (500μl) was heated at reflux for 30 minutes. After cooling, the volatiles were removed by evaporation. The residue was partitioned between methylene chloride and saturated aqueous sodium hydrogen carbonate and the aqueous layer was adjusted to pH8 with solid sodium hydrogen carbonate. The organic layer was washed with water, brine, dried (MgSO₄) and the volatiles were removed by evaporation. The residue was triturated with ether, collected by filtration, washed with ether and dried under vacuum to give 4-chloro-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (1.4g, 65%).

¹H NMR Spectrum: (DMSO-d₆) 2.1(m, 2H); 2.2(s, 3H); 2.3-2.5(m, 10 H); 4.05(s, 3H); 4.3(t, 2H); 7.4(s, 1H); 7.45(s, 1H); 8.88(s, 1H)

Example 15

The following illustrate representative pharmaceutical dosage forms containing the compound of formula I, or a pharmaceutically acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

98/022

- 61 -

5	(a)	<u>Tablet I</u>	<u>mg/tablet</u>
		Compound X	100
		Lactose Ph.Eur	182.75
		Croscarmellose sodium	12.0
		Maize starch paste (5% w/v paste).....	2.25
		Magnesium stearate.....	3.0
10	(b)	<u>Tablet II</u>	<u>mg/tablet</u>
		Compound X	50
		Lactose Ph.Eur	223.75
		Croscarmellose sodium	6.0
		Maize starch	15.0
		Polyvinylpyrrolidone (5% w/v paste).....	2.25
		Magnesium stearate.....	3.0
15	(c)	<u>Tablet III</u>	<u>mg/tablet</u>
		Compound X	1.0
		Lactose Ph.Eur	93.25
		Croscarmellose sodium	4.0
		Maize starch paste (5% w/v paste).....	0.75
		Magnesium stearate.....	1.0
20	(d)	<u>Capsule</u>	<u>mg/capsule</u>
		Compound X	10
		Lactose Ph.Eur	488.5
		Magnesium stearate.....	1.5
25	(e)	<u>Injection I</u>	<u>(50 mg/ml)</u>
		Compound X	5.0% w/v
		1N Sodium hydroxide solution	15.0% v/v
		0.1N Hydrochloric acid	
		(to adjust pH to 7.6)	
30		Polyethylene glycol 400	4.5% w/v

- 62 -

Water for injection to 100%

(f) Injection II 10 mg/ml)

Compound X 1.0% w/v

5 Sodium phosphate BP 3.6% w/v

0.1N Sodium hydroxide solution 15.0% v/v

Water for injection to 100%

(g) Injection III (1mg/ml,buffered to pH6)

10 Compound X 0.1% w/v

Sodium phosphate BP 2.26% w/v

Citric acid 0.38% w/v

Polyethylene glycol 400 3.5% w/v

Water for injection to 100%

15

Note

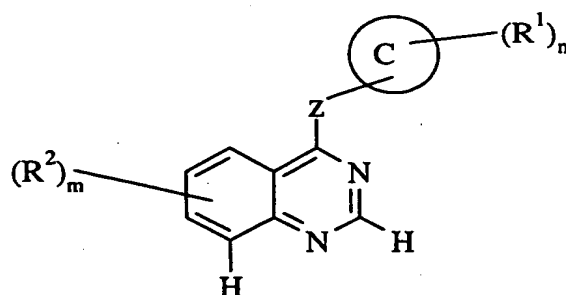
The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

98/022

- 63 -

CLAIM:

1. The use of compounds of the formula I:



(I)

wherein:

ring C is a 5-6-membered heterocyclic moiety which may be saturated or unsaturated, which may be aromatic or non-aromatic, and which contains 1-3 heteroatoms selected independently from O, N and S;

Z is -O-, -NH-, -S- or -CH₂-;

R¹ represents hydrogen, C₁₋₄alkyl, C₁₋₄alkoxymethyl, di(C₁₋₄alkoxy)methyl,

C₁₋₄alkanoyl, trifluoromethyl, cyano, amino, C₂₋₅alkenyl, C₂₋₅alkynyl, a phenyl group, a benzyl group or a 5-6-membered heterocyclic group with 1-3 heteroatoms, selected independently

from O, S and N, which heterocyclic group may be aromatic or non-aromatic and may be saturated (linked via a ring carbon or nitrogen atom) or unsaturated (linked via a ring carbon atom), and which phenyl, benzyl or heterocyclic group may bear on one or more ring carbon atoms up to 5 substituents selected from hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, cyano, amino, nitro, C₂₋₄alkanoyl, C₁₋₄alkanoylamino, C₁₋

4alkoxycarbonyl, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphinyl, C₁₋₄alkylsulphonyl, carbamoyl, N-C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl, N,N-di(C₁₋₄alkyl)aminosulphonyl, C₁₋₄alkylsulphonylamino, and a saturated heterocyclic group selected from morpholino, thiomorpholino, pyrrolidiny, piperaziny, piperidiny, imidazolidiny and pyrazolidiny, which saturated heterocyclic group may bear 1 or 2

substituents selected from oxo, hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, cyano, amino, nitro and C₁₋₄alkoxycarbonyl;

n is an integer from 0 to 5;

m is an integer from 0 to 3;

R^2 represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylsulphonyl, $-NR^3R^4$ (wherein R^3 and R^4 , which may be the same or different, each represents hydrogen or C_{1-3} alkyl), or R^5X^1 (wherein X^1 represents a direct bond, -O-, -CH₂-, -OCO-, carbonyl, -S-, -SO-, -SO₂-, -NR⁶CO-, -CONR⁷-, -SO₂NR⁸-, -NR⁹SO₂- or -NR¹⁰- (wherein R^6 , R^7 , R^8 , R^9 and R^{10} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxyC₂₋₃alkyl), and R^5 is selected from one of the following eighteen groups:

- 1) hydrogen or C_{1-5} alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino;
- 10 2) C_{1-5} alkylX²COR¹¹ (wherein X² represents -O- or -NR¹²- (in which R^{12} represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxyC₂₋₃alkyl) and R^{11} represents C_{1-3} alkyl, -NR¹³R¹⁴ or -OR¹⁵ (wherein R^{13} , R^{14} and R^{15} which may be the same or different each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxyC₂₋₃alkyl));
- 15 3) C_{1-5} alkylX³R¹⁶ (wherein X³ represents -O-, -S-, -SO-, -SO₂-, -OCO-, -NR¹⁷CO-, -CONR¹⁸-, -SO₂NR¹⁹-, -NR²⁰SO₂- or -NR²¹- (wherein R^{17} , R^{18} , R^{19} , R^{20} and R^{21} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxyC₂₋₃alkyl) and R^{16} represents hydrogen, C_{1-3} alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3} alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4} alkoxy and which cyclic group may
- 20 bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl and C_{1-4} alkoxy);
- 4) C_{1-5} alkylX⁴C₁₋₅alkylX⁵R²² (wherein X⁴ and X⁵ which may be the same or different are each -O-, -S-, -SO-, -SO₂-, -NR²³CO-, -CONR²⁴-, -SO₂NR²⁵-, -NR²⁶SO₂- or -NR²⁷- (wherein R^{23} , R^{24} , R^{25} , R^{26} and R^{27} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxyC₂₋₃alkyl) and R^{22} represents hydrogen or C_{1-3} alkyl);
- 25 5) R²⁸ (wherein R²⁸ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} alkoxyC₁₋₄alkyl and C_{1-4} alkylsulphonylC₁₋₄alkyl);
- 30 6) C_{1-5} alkylR²⁸ (wherein R²⁸ is as defined hereinbefore);
- 7) C_{2-5} alkenylR²⁸ (wherein R²⁸ is as defined hereinbefore);
- 8) C_{2-5} alkynylR²⁸ (wherein R²⁸ is as defined hereinbefore);

98/022

- 65 -

- 9) R^{29} (wherein R^{29} represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents on an available carbon atom selected from hydroxy, halogeno, amino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, trifluoromethyl, cyano, $-\text{CONR}^{30}\text{R}^{31}$ and $-\text{NR}^{32}\text{COR}^{33}$ (wherein R^{30} , R^{31} , R^{32} and R^{33} , which may be the same or different, each represents hydrogen, C_{1-4} alkyl or C_{1-3} alkoxy C_{2-3} alkyl));
- 10) C_{1-5} alkyl R^{29} (wherein R^{29} is as defined hereinbefore);
- 11) C_{2-5} alkenyl R^{29} (wherein R^{29} is as defined hereinbefore);
- 12) C_{2-5} alkynyl R^{29} (wherein R^{29} is as defined hereinbefore);
- 13) C_{1-5} alkyl X^6R^{29} (wherein X^6 represents $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{NR}^{34}\text{CO}-$, $-\text{CONR}^{35}-$, $-\text{SO}_2\text{NR}^{36}-$, $-\text{NR}^{37}\text{SO}_2-$ or $-\text{NR}^{38}-$ (wherein R^{34} , R^{35} , R^{36} , R^{37} and R^{38} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{29} is as defined hereinbefore);
- 14) C_{2-5} alkenyl X^7R^{29} (wherein X^7 represents $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{NR}^{39}\text{CO}-$, $-\text{CONR}^{40}-$, $-\text{SO}_2\text{NR}^{41}-$, $-\text{NR}^{42}\text{SO}_2-$ or $-\text{NR}^{43}-$ (wherein R^{39} , R^{40} , R^{41} , R^{42} and R^{43} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{29} is as defined hereinbefore);
- 15) C_{2-5} alkynyl X^8R^{29} (wherein X^8 represents $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{NR}^{44}\text{CO}-$, $-\text{CONR}^{45}-$, $-\text{SO}_2\text{NR}^{46}-$, $-\text{NR}^{47}\text{SO}_2-$ or $-\text{NR}^{48}-$ (wherein R^{44} , R^{45} , R^{46} , R^{47} and R^{48} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{29} is as defined hereinbefore);
- 16) C_{1-3} alkyl X^9C_{1-3} alkyl R^{29} (wherein X^9 represents $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{NR}^{49}\text{CO}-$, $-\text{CONR}^{50}-$, $-\text{SO}_2\text{NR}^{51}-$, $-\text{NR}^{52}\text{SO}_2-$ or $-\text{NR}^{53}-$ (wherein R^{49} , R^{50} , R^{51} , R^{52} and R^{53} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{29} is as defined hereinbefore); and
- 17) C_{1-3} alkyl X^9C_{1-3} alkyl R^{28} (wherein X^9 and R^{28} are as defined hereinbefore);
- and salts thereof, and prodrugs thereof for example esters, amides and sulphides, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

This Page Blank (uspto)

98/022

ABSTRACT OF THE DISCLOSURE

- 5 The present invention relates to quinazoline derivatives, processes for their preparation, pharmaceutical compositions containing them as active ingredient, methods for the treatment of disease states associated with angiogenesis and/or increased vascular permeability, to their use as medicaments and to their use in the manufacture of medicaments for use in the production of antiangiogenic and/or
- 10 vascular permeability reducing effects in warm-blooded animals such as humans.

This Page Blank (uspto)